

Department:	Pharmacy Management	Original Approval:	12/24/2015
Policy #:	PM119	Last Approval:	09/19/2018
Title:	Nivolumab (Opdivo®)		
Approved By:	UM Committee		

REQUIRED CLINICAL DOCUMENTATION FOR REVIEW

Documentation required to determine medical necessity for Nivolumab (Opdivo): History and/or physical examination notes and relevant specialty consultation notes that address the problem and need for the service: -Diagnosis - Medication list (current and past) to include start and end dates of previous trials for all chemotherapy regimens -Prescribed by or in consultation with an oncologist -Dosing and duration requested -Age -Weight -Labs/diagnostics as indicated per diagnosis.

BACKGROUND

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

- 1) Patients with unresectable or metastatic melanoma:
 - For use as a single agent in patients with *BRAF V600* wild-type melanoma; AND
 - For use as a single agent in patients with *BRAF V600* mutation positive melanoma. This indication was approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials; AND
 - For use in combination with Yervoy® (ipilimumab intravenous injection) in patients with melanoma. This indication was approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials; AND
- 2) Patients with melanoma with lymph node involvement or metastatic disease who have undergone complete resection, in the adjuvant setting;* AND
- 3) Metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. Patients with epidermal growth factor receptor (*EGFR*) or anaplastic lymphoma kinase (*ALK*) genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Opdivo; AND
- 4) Patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy.
- 5) Patients with intermediate or poor risk, previously untreated advanced RCC, in combination with Yervoy; AND
- 6) Adult patients with classical Hodgkin lymphoma (cHL) that has relapsed or progressed after autologous hematopoietic stem cell transplantation (auto-HSCT) and Adcetris® (brentuximab vedotin intravenous injection) or three or more lines of systemic therapy that includes auto-

of therapy. For recurrent, unresectable, or metastatic head and neck cancers (with no surgery or radiation therapy option), first-line therapies for non-nasopharyngeal cancer are as follows: cisplatin or carboplatin plus 5-FU and Erbitux (category 1); cisplatin or carboplatin with Erbitux plus docetaxel or paclitaxel; or Erbitux. For either non-nasopharyngeal or nasopharyngeal cancer, first-line therapies include cisplatin or carboplatin plus docetaxel or paclitaxel; cisplatin plus 5-FU; and many single-agent therapies (e.g., cisplatin, carboplatin, paclitaxel, docetaxel, 5-FU, MTX, capecitabine). Single-agent therapy with Keytruda or Opdivo is recommended for disease progression on or after platinum-containing chemotherapy.

Efficacy of Opdivo was studied in one Phase III, multicenter, open-label trial (CHECKMATE 141) in patients with recurrent or metastatic HNSCC whose disease had progressed within 6 months of receiving platinum-based chemotherapy for adjuvant, neo-adjuvant, primary (unresectable locally advanced) or metastatic disease.^{1,8} Patients (n = 361) were randomized (2:1) to receive intravenous Opdivo 3 mg/kg (n = 240) once every 2 weeks or to investigator choice of standard, single-agent systemic therapy with MTX (n=52), docetaxel (n=54), or Erbitux (n=15) until disease progression or unacceptable toxicity. Nivolumab could be continued beyond disease progression. The primary endpoint was overall survival. **Results** are from a pre-specified interim analysis after about 278 deaths had occurred. Median overall survival was 7.5 months (95% CI: 5.5, 9.1) in the Opdivo group vs. 5.1 months (95% CI: 4.0, 6.0) in the group receiving standard therapy; hazard ration (HR) for death was 0.70 (95% CI: 0.52, 0.92; P = 0.01).¹ PFS was not significantly different between the two groups.

Dosing in HNSCC in Adults. Dosing must meet ONE of the following (A OR B):¹

- a. As a single agent, 240 mg as an intravenous infusion over 30 minutes once every 2 weeks; OR
- b. As a single agent, 480 mg as an intravenous infusion over 30 minutes once every 4 weeks.

The recommended dose is 240 mg every 2 weeks or 480 mg every 4 weeks given as an intravenous infusion over 30 minutes until disease progression or unacceptable toxicity.¹ Management of AEs may require that Opdivo be withheld or permanently discontinued as determined by the prescribing physician.

Initial Approval/Extended Approval.

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

Duration of Therapy in HNSCC. Indefinite if the patient is responding to therapy.

Labs/Diagnostics. None required.

2. Classical Hodgkin Lymphoma (cHL).

Criteria. The patient must meet the following criteria (A, B, C, D, AND E):

- A) Opdivo is prescribed by or in consultation with an oncologist; AND
- B) Opdivo is being used as single-agent therapy; AND
- C) The patient has relapsed or progressive disease;¹ AND

- D) The patient is ≥ 18 years of age;² AND
- E) ONE the following conditions applies (i, ii, or iii):²
- i. The patient has had an autologous hematopoietic stem cell transplantation (auto-HSCT) and post-transplant therapy with Adcetris (brentuximab vedotin intravenous injection); OR
 - ii. The patients has had three or more lines of systemic therapy (e.g., ABVD [doxorubicin, bleomycin, vinblastine, and dacarbazine], Sanford V [doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin, and prednisone], escalated BEACOPP [bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone]) AND this includes an auto-HSCT as one line of therapy; OR
 - iii. The patient is not eligible for transplant according to the prescribing physician.

Opdivo is indicated in adult patients with cHL that has relapsed or progressed after auto-HSCT and Adcetris or three or more lines of systemic therapy that includes auto-HSCT.¹ This indication is approved under accelerated approval based on ORR.

The National Comprehensive Cancer Network (NCCN) clinical practice guidelines on Hodgkin lymphoma (version 3.2018) recommend Opdivo as a subsequent systemic therapy option as a single agent in patients aged ≥ 18 years with cHL for relapsed or refractory disease following auto-HSCT and Adcetris or following three or more lines of systemic therapy that includes auto-HSCT.² As a general guideline, the checkpoint inhibitors (Opdivo or Keytruda® [pembrolizumab intravenous injection]) are commonly recommended for patients with refractory cHL who are ineligible for a transplant based on comorbidity or failure of first salvage chemotherapy OR in any patient who has relapsed after auto-HSCT with or without Adcetris. Post-allogeneic transplant, patients can receive either Opdivo or Keytruda, but there are limited data for this use. In patients with cHL who are > 60 years of age, Opdivo, as a single agent, is recommended as one of the options for palliative therapy for relapsed or refractory disease. As outcomes are poor for these patients, no uniform recommendation can be made, but clinical trials or possibly single-agent therapy for palliation is recommended.

Two studies evaluated the efficacy of Opdivo in patients with cHL after failure of auto-HSCT and post-transplant therapy with Adcetris.¹ CHECKMATE-205 was a single-arm, open-label, multicenter, multicohort study, and the other, CHECKMATE-039, was an open-label, multicenter, dose escalation study. Efficacy was evaluated by ORR determined by an independent radiographic review committee (IRRC). Efficacy was evaluated in 95 patients in the two trials combined who had received Adcetris after failure of auto-HSCT. **Results.** The ORR was 66% (95% confidence interval [CI]: 56%, 66%) with 6% of patients ($n = 6/95$) having a complete remission and 60% of patients ($n = 57/95$) having a partial remission. Median duration of response was 13.1 months (95% CI: 9.5, not estimable). Efficacy was also evaluated in 258 patients in CHECKMATE-205 and CHECKMATE-039 combined who had relapsed or progressive cHL after auto-HSCT. In all, 76% ($n = 195/258$) of patients had prior Adcetris therapy with 78% receiving Adcetris only after auto-HSCT, 17% received Adcetris only before transplantation, and 5% receiving it both before and after HSCT. Median duration of therapy with Opdivo was 10 months. **Results.** The ORR was 69% (95% CI: 63%, 75%); 14% of patients had a complete remission and 55% had

a partial remission. Median duration of response was not estimable. The estimated median duration of partial remission was 13.1 months and median duration of complete remission was not reached.

In the CheckMate-205 trial (published), patients with relapsed/refractory cHL after auto-HCT treatment failure were divided into three cohorts by treatment history: Adcetris-naïve (cohort A), Adcetris received after auto-HSCT (cohort B), and Adcetris received before and/or after auto-HSCT (cohort C).³ Patients received Opdivo 3 mg/kg every 2 weeks until disease progression or unacceptable toxicity. The primary endpoint was ORR per IRRC. **Results.** In all, 243 patients were treated, n = 63 in cohort A, n = 80 in cohort B, and n = 100 in cohort C. After a median follow-up of 18 months, 40% continued to receive treatment. The ORR was 69% (95% CI: 63%, 75%) overall with 16% of patients achieving a complete remission and 53% achieving a partial remission. Overall, the median duration of response was 16.6 months (95% CI: 13.2, 20.3), and median PFS was 14.7 months (95% CI: 11.3, 18.5). In the 70 patients treated past conventional disease progression, 61% of those evaluable had stable or further reduced target tumor burdens.

Dosing in Classic Hodgkin Lymphoma in Patients ≥ 18 years of age. Dosing must meet ONE of the following (A OR B):

- A) As a single agent, 240 mg as an intravenous infusion over 30 minutes once every 2 weeks;¹ OR
- B) As a single agent, 480 mg as an intravenous infusion over 30 minutes once every 4 weeks.¹

The recommended dose is 240 mg every 2 weeks or 480 mg every 4 weeks given as an intravenous infusion over 30 minutes until disease progression or unacceptable toxicity.¹ Management of AEs may require that Opdivo be withheld or permanently discontinued as determined by the prescribing physician.

Initial Approval/Extended Approval.

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

Duration of Therapy in Classical Hodgkin Lymphoma. Indefinite if the patient is responding to therapy.

Labs/Diagnostics. None required.

3. Hepatocellular Carcinoma (HCC).

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 tried Nexavar (sorafenib tablets);^{1,9} AND
- C) Opdivo will be used as a single agent.⁹

The NCCN guidelines on hepatobiliary cancers (version 2.2018)⁶ recommend Opdivo for treatment of HCC (adenocarcinoma) as a single agent if there is progression on or after Nexavar for patients (Child-Pugh Class A or B7 only) who are non-transplant candidates with unresectable disease; are inoperable by performance status or comorbidity (local disease or local disease with minimal

extrahepatic disease only); or have extensive liver tumor burden or metastatic disease (category 2A).

In one Phase I/II, open-label, multicenter, dose escalation and expansion trial (CHECKMATE-040), adults with advanced HCC with or without hepatitis C or B virus (HCV or HBV) infection received Opdivo.¹⁰ In the dose escalation phase, patients (n = 48) received Opdivo 0.1 to 10 mg/kg every 2 weeks. In the dose expansion phase, Opdivo 3 mg/kg was given every 2 weeks to patients (n = 214) in four cohorts: Nexavar untreated or intolerant without viral hepatitis, Nexavar progressor without viral hepatitis, HCV infected, and HBV infected. In all, 77% of patients (n = 202/262) completed treatment and follow-up is continuing. In the dose escalation phase no maximum tolerated dose was reached; 88% of patients (n = 42/48) discontinued due to disease progression. In the 214 patients treated in the dose expansion phase, the ORR was 20% (95% CI: 15%, 26%); median duration of response was 9.9 months. In the dose expansion phase in patients who progressed on or were intolerant to Nexavar (n = 154), 31% had active HBV infection, 21% had active HCV infection, and 49% had no evidence of active HBV or HCV.¹ Efficacy was assessed by blinded independent central review. The ORR was 14.3% (n = 22/154; 95% CI: 9.2%, 20.8%); 3 patients had a CR and 19 patients had a PR. Duration of response was 3.2 to 38.2+ months.

Dosing in Hepatocellular Carcinoma in Adults.

*Dosing must meet ONE of the following (A OR B):*¹

- a. As a single agent, 240 mg as an intravenous infusion over 30 minutes once every 2 weeks; OR
- b. As a single agent, 480 mg as an intravenous infusion over 30 minutes once every 4 weeks.

The recommended dose is 240 mg every 2 weeks or 480 mg every 4 weeks given as an intravenous infusion over 30 minutes until disease progression or unacceptable toxicity.¹ Management of AEs may require that Opdivo be withheld or permanently discontinued as determined by the prescribing physician.

Initial Approval/Extended Approval.

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

Duration of Therapy in Hepatocellular Carcinoma. Indefinite if the patient is responding to therapy.

Labs/Diagnostics. None required.

4. 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) ONE of the following (i or ii) applies:
 - i. The patient has unresectable, advanced (including Stage III or IV disease), or metastatic melanoma; OR

- ii. Opdivo is being given for adjuvant therapy in a patient with melanoma with lymph node involvement or metastatic disease and has undergone complete resection.

The NCCN guidelines on melanoma (version 2.2018) recommend Opdivo for the following uses:¹¹

- Adjuvant therapy as a single agent for:
 - Resected Stage IIIB/C sentinel node positive disease following active nodal basin surveillance or complete lymph node dissection (preferred immunotherapy regimen) [category 1]; or
 - Stage III disease with clinically positive node(s) following wide excision of primary tumor and complete therapeutic lymph node dissection (preferred immunotherapy regimen) [category 1]; or
 - Stage III disease with clinical satellite or in-transit metastases if no evidence of disease post surgery (category 2A); or
 - Local, satellite and/or in-transit recurrence if no evidence of disease post surgery (category 2A); or
 - Following complete lymph node dissection and/or complete resection of nodal recurrence (preferred immunotherapy regimen) [category 1].
- Adjuvant treatment of distant metastatic disease after complete resection with no evidence of disease (category 1).
- Therapy for metastatic or unresectable disease as a single agent or in combination with Yervoy as:
 - First-line therapy (category 1); or
 - Second-line or subsequent therapy after disease progression or maximum clinical benefit from BRAF targeted therapy if anti PD-1 therapy (either alone or in combination with Yervoy) not previously (category 2A); or
 - Second-line or subsequent therapy after disease progression or maximum clinical benefit from BRAF targeted therapy if prior anti-PD-1 therapy (either alone or in combination with Yervoy) resulted in disease control (CR, PR, or stable disease) and no residual toxicity, and disease progression/relapse occurred > 3 months after treatment discontinuation (category 2A).

Opdivo/Yervoy combination therapy is associated with improved ORR and PFS compared with single-agent Yervoy, at the expense of significantly increased toxicity.

Regarding Opdivo's recommendation as a preferred *adjuvant* immunotherapy regimen, the NCCN melanoma panel states that Opdivo has shown a clinically significant improvement in relapse free survival (RFS) compared with high-dose Yervoy (10 mg/kg), but its impact on overall survival has not yet been reported.¹¹ Most panel members prefer adjuvant Opdivo over high-dose Yervoy based on improved efficacy and less toxicity, even without reported overall survival data. (See CHECKMATE-238 study below.)

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).^{1,12} Patients were randomized to receive Opdivo 3 mg/kg every 2 weeks or investigator's

choice of chemotherapy (ICC). In a pre-planned interim analysis after 120 patients received treatment with Opdivo for 6 months, the ORR was 32% (95% CI: 23%, 41%). In all, 268 patients received Opdivo and 102 received ICC.¹³ A higher proportion of patients who were randomized to receive ICC did not receive treatment compared with those randomized to Opdivo. With a follow-up of 2 years, median duration of therapy was 4.7 months for Opdivo and 2.0 months with ICC. Median overall survival was 15.7 months for the Opdivo group vs. 14.4 months for the ICC group. The authors note that overall survival results should be interpreted with caution as it was likely impacted by an increased dropout rate before treatment, which led to crossover of the ICC group, and by an increased proportion of patients in the Opdivo group with poor prognostic factors.

In the Phase III CHECKMATE-066 trial, patients (n = 418) with previously untreated *BRAF V600* wild-type unresectable or metastatic melanoma were randomized to receive Opdivo every 2 weeks or dacarbazine every 3 weeks.^{1,14} An interim analysis based on 47% of the total planned events for overall survival showed a statistically significant improvement in overall survival. Median overall survival was not reached in the Opdivo group and was 10.8 months in the dacarbazine arm (HR 0.42; 95% CI: 0.30, 0.60; P < 0.0001). Median PFS was 5.1 months with Opdivo vs. 2.2 months with dacarbazine.

In one Phase III study (CHECKMATE-067), Opdivo plus Yervoy (n = 314) was compared with Opdivo monotherapy (n = 316) and Yervoy monotherapy (n = 315) in patients with previously untreated, unresectable or metastatic Stage III or IV melanoma.^{1,15} **Results.** Median PFS was 11.5 months with combination therapy vs. 2.9 months with Yervoy monotherapy vs. 6.9 months with Opdivo monotherapy. With a minimum follow-up of 36 months, median overall survival had not been reached in the Opdivo plus Yervoy group (95% CI: 38.2 months, not reached) and was 37.6 months in the Opdivo monotherapy group vs. 19.9 months in the Yervoy monotherapy patients.¹⁶ The HR for death with Opdivo plus Yervoy vs. Yervoy was 0.55; the HR for death with Opdivo vs. Yervoy was 0.65. The overall survival rate at 3 years was 58% for the Opdivo plus Yervoy group, 52% for the Opdivo group, and 34% for the Yervoy group. Treatment-related Grade 3 or 4 AEs occurred in 59% of patients on Opdivo plus Yervoy, 21% of patients on Opdivo, and 28% on Yervoy.

In another Phase III trial (CHECKMATE-238), 906 patients (≥ 15 years of age) who were undergoing complete resection of Stage IIIB, IIIC, or IV melanoma were randomized to receive either Opdivo 3 mg/kg every 2 weeks or Yervoy 10 mg/kg every 3 weeks for 4 doses and then every 12 weeks.¹⁷ Patients were treated for up to 1 year or until disease recurrence, or unacceptable toxicity. After a minimum follow-up of 18 months, the 12-month RFS was 70.5% (95% CI: 66.1%, 74.5%) in the Opdivo group and 60.8% (95% CI: 56.0%, 65.2%) in the Yervoy group (HR for disease recurrence or death 0.65; 97.56% CI: 0.51, 0.83; P < 0.001). Treatment-related Grade 3 or 4 AEs were reported in 14.4% of patients on Opdivo and in 45.9% of patients on Yervoy. Treatment was discontinued because of AEs in 9.7% and 42.6% of patients on Opdivo and Yervoy, respectively.

Dosing in Advanced (including Stage III or IV disease), Unresectable or Metastatic Melanoma in Adults.
Dosing must meet ONE of the following (A OR B):

A) Unresectable or Metastatic Melanoma.

- i. As a single agent, 240 mg every 2 weeks as an intravenous infusion over 30 minutes; OR
- ii. As a single agent, 480 mg every 4 weeks as an intravenous infusion over 30 minutes; OR
- iii. When used in combination with Yervoy, Opdivo 1 mg per kg once every 3 weeks as an intravenous infusion over 30 minutes for up to 4 doses.

B) Adjuvant Treatment of Melanoma.

- i. As a single agent, 240 mg every 2 weeks as an intravenous infusion over 30 minutes; OR
- ii. As a single agent, 480 mg every 4 weeks as an intravenous infusion over 30 minutes.

When used for unresectable or metastatic melanoma as a single agent, the recommended dose is 240 mg every 2 weeks or 480 mg every 4 weeks given as an intravenous infusion over 30 minutes until disease progression or unacceptable toxicity.¹ When Opdivo is used in combination with Yervoy for unresectable or metastatic melanoma, the recommended dose is 1 mg/kg every 3 weeks for 4 doses, then 240 mg once every 2 weeks or 480 mg every 4 weeks as a single agent until disease progression or unacceptable toxicity. When used for adjuvant treatment of melanoma the recommended dose is 240 mg every 2 weeks or 480 mg every 4 weeks given as an intravenous infusion over 30 minutes until disease recurrence or unacceptable toxicity for up to 1 year. Management of AEs may require that Opdivo be withheld or permanently discontinued as determined by the prescribing physician.¹

Initial Approval/Extended Approval.

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

B) *Extended Approval:*

For unresectable or metastatic melanoma, approve at 6-month intervals if the patient has a response as determined by the prescribing physician.

For adjuvant therapy of melanoma, approve up to a total of 12 months.

C)

Duration of Therapy in Melanoma in Adults.

For unresectable or metastatic melanoma, indefinite if the patient is responding to therapy.

For adjuvant therapy of melanoma, approve for up to 12 months total.

In one trial where Opdivo was used as adjuvant therapy, the median number of 3 mg/kg doses was 24.¹⁷

Labs/Diagnostics. None required.

5. Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Colorectal Cancer (CRC).

Criteria. *The patient must meet the following criteria (A, B, C, D, E, AND F):*

- a. Opdivo is prescribed by or in consultation with an oncologist; AND
- b. The patient has unresectable, advanced, or metastatic colorectal cancer (CRC)¹⁸⁻¹⁹; AND
- c. The patient is 12 years of age or greater;¹ AND
- d. Opdivo will be used as a single agent;^{1,18-19} AND

- e. The colorectal cancer is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR);^{1,26-27} AND
- f. One of the following applies (i, ii, or iii):⁸⁻¹⁹
- i. The patient's colorectal cancer (CRC) has progressed after treatment with a fluoropyrimidine (e.g., 5-fluorouracil [5-FU], capecitabine), oxaliplatin, or irinotecan AND the patient has not previously been treated with Keytruda (pembrolizumab) or Opdivo; OR
 - ii. The patient has had adjuvant therapy with FOLFOX (5-fluorouracil [5-FU], leucovorin, and oxaliplatin) OR CapeOX (capecitabine and oxaliplatin); OR
 - iii. The patient is not a candidate for intensive therapy, according to the prescribing physician.

The NCCN guidelines on colon cancer (version 2.2018)¹⁸ and rectal cancer (version 1.2018)¹⁹ recommend Opdivo for adenocarcinoma as:

- primary treatment as a single agent for unresectable metachronous metastases (dMMR/MSI-H only) and previous adjuvant FOLFOX or CapeOX within the past 12 months (category 2A); or
- initial therapy as a single agent for patients with unresectable advanced or metastatic disease (dMMR/MSI-H only) who are not appropriate for intensive therapy (category 2A); or
- subsequent therapy as a single agent (if Opdivo or Keytruda not previously given) for unresectable advanced or metastatic disease (dMMR/MSI-H only) following previous oxaliplatin-irinotecan- and/or fluoropyrimidine-based therapy (category 2A).

The NCCN guidelines panel recommends universal MMR and MSI testing for all patients with a personal history of colon or rectal cancer to identify patients with Lynch syndrome, to inform use of immunotherapy in patients with metastatic disease, and to inform decisions for patients with Stage II disease.

CHECKMATE-142 was an open-label, multicenter Phase II trial in adults (n = 74) with MSI-H or dMMR recurrent or metastatic CRC who had progressed on or after, or had been intolerant of, at least one previous line of treatment including a fluoropyrimidine and oxaliplatin or irinotecan.²⁰ Patients received Opdivo 3 mg/kg every 2 weeks until disease progression, death, unacceptable toxicity, or withdrawal from the study. Fifty-four percent (54%) of the patients had received ≥ three previous treatments. With a median follow-up of 12 months, 31.1% of patients (n = 23/74; 95% CI: 20.8%, 42.9%) attained an investigator assessed objective response (all were PRs), and 69% of patients had disease control for 12 weeks or longer. Median duration of response was not reached. Results from IRRC showed an ORR of 32% (95% CI: 22%, 44%) in all patients, and an ORR of 28% (95% CI: 17%, 42%) in the 53 patients with prior treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.¹

In the CheckMate-142 trial, another cohort of patients with MSI-H or dMMR recurrent or metastatic CRC (n = 119) received Opdivo 3 mg/kg and Yervoy 1 mg/kg once every 3 weeks for four doses and then Opdivo 3 mg/kg once every 2 weeks until disease progression, discontinuation due to toxicity, death, withdrawal of consent, or study end.⁸ At data cutoff, median duration of follow-up was 13.4 months. In the 119 patients, the ORR was 54.6% (95% CI: 45.2%, 63.8%) per investigator assessment. There were CRs in 3.4% of patients (n = 4) and PRs in 51.3% (n = 61). Disease control

for ≥ 12 weeks was achieved in 80% of patients ($n = 95/119$). PFS and overall survival results were not mature.

Efficacy and safety of Opdivo in pediatric patients ≥ 12 years of age with MSI-H or dMMR metastatic CRC that progressed after treatment with fluoropyrimidine, oxaliplatin, and irinotecan is supported by evidence in adults and with additional population pharmacokinetics data showing that age and body weight had no clinically meaningful effect on exposure of Opdivo.¹ Drug exposure is generally similar between adults and children ≥ 12 years of age for monoclonal antibodies. The course of MSI-H or dMMR metastatic CRC is similar enough to allow extrapolation of data from adults to pediatric patients.

Dosing in MSI-H or dMMR Colorectal Cancer in Adults and Children at least 12 years of age.

Dosing must meet the following: As a single agent, 240 mg as an intravenous infusion over 30 minutes once every 2 weeks.^{1,18}

The recommended dose in adults and children ≥ 12 years of age is 240 mg given as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity.¹ Management of AEs may require that Opdivo be withheld or permanently discontinued as determined by the prescribing physician.

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 MSI-H or dMMR Colorectal Cancer. Indefinite if the patient is responding to therapy.

Labs/Diagnostics. Identification of MSI-H or dMMR tumor status is required before initiating therapy with Opdivo.

6. Non-Small Cell Lung Cancer (NSCLC).

Criteria. The patient must meet the following criteria (A, B, C, D, E and F):

- A) Opdivo is prescribed by or in consultation with an oncologist; AND
- B) The patient has metastatic disease; AND
- C) The patient has tried systemic chemotherapy (e.g., cisplatin, carboplatin, Alimta [pemetrexed injection], Abraxane [paclitaxel albumin-bound injection], gemcitabine, paclitaxel); AND
- D) The patient has not previously been treated with Keytruda, Opdivo, or Tecentriq (atezolizumab injection for intravenous use); AND
- E) Opdivo will be used as a single agent; AND
- F) The patient has one of the following histologic subtypes of NSCLC (i or ii):
 - i. Non-squamous cell carcinoma (that is, adenocarcinoma, large cell, or NSCLC not otherwise specified) AND the following condition is met (a):

- a) Testing has been completed for epidermal growth factor receptor (*EGFR*) mutations and anaplastic lymphoma kinase (*ALK*) fusions, AND the patient meets the ONE of the following (1 or 2):
- (1) The patient's tumor is sensitizing *EGFR* mutation positive or *ALK* positive and the patient has received targeted drug therapy for the specific mutation; OR
 - (2) *EGFR* and *ALK* tests are negative;

OR

- ii. Squamous cell carcinoma.

The NCCN guidelines for NSCLC (version 4.2018) recommend Opdivo as a preferred single-agent therapy (if Keytruda has not already been given) as *subsequent therapy* for patients with metastatic NSCLC with performance status 0 to 2 who 1) have progressed on a first-line initial cytotoxic regimen (category 1) or 2) for further progression on other systemic therapy if not previously given (category 2A).²¹ These guidelines recommend Opdivo for adenocarcinoma (with mixed subtypes), squamous cell carcinoma, and large cell carcinoma (i.e., either squamous and non-squamous cell NSCLC).

In patients with metastatic non-squamous cell NSCLC or NSCLC not otherwise specified, the NCCN guidelines recommend testing for *EGFR* mutations and *ALK* gene rearrangements (category 1) so that patients with genetic abnormalities can receive therapy with targeted agents.²¹ Testing for *ROS1* rearrangements, *BRAF* mutations, and PD-L1 expression is also recommended (all are category 2A recommendations). Testing for *EGFR* mutations and *ALK* rearrangements, can be considered in patients with squamous cell histology if they are never smokers, small biopsy specimens were used for testing, or mixed histology was reported. In patients with squamous cell carcinoma, *ROS1* and *BRAF* also should be considered. *EGFR*, *ALK*, and *ROS1* genetic alterations do not usually overlap. *BRAF* mutations typically do not overlap with *EGFR* mutations or *ALK* rearrangements. PD-L1 testing is recommended before first-line treatment in patients with metastatic NSCLC with negative or unknown test results for *EGFR* mutations, *ALK* rearrangements, *BRAF* V600E mutations, and *ROS1* rearrangements. Currently, testing for PD-L1 expression is the best available biomarker to assess whether a patient is a candidate for Keytruda therapy. Testing for PD-L1 is not required for using Opdivo or Tecentriq for subsequent therapy. Regardless of PD-L1 expression levels, immunotherapy seems to be less effective in tumors with an actionable mutation (e.g., *EGFR* mutations, *ALK* rearrangements). The NCCN panel strongly advises broader molecular profiling to identify rare driver mutations to ensure that patients receive appropriate therapy.

Subsequent therapy. In patients with performance status of 0 to 2 who have progressive disease, subsequent therapy with one of the systemic immune checkpoint inhibitor is a preferred therapy, Opdivo, Keytruda, or Tecentriq (all are category 1) if Keytruda was not previously given.²¹ Other subsequent systemic therapies in patients with performance status 0 to 2 and progressive disease include docetaxel, Alimta® (pemetrexed for intravenous injection) [for non-squamous cell histology only], or gemcitabine, or the combination of Cyramza® (ramucirumab injection for intravenous use) and docetaxel. Other regimens are also recommended for further progression and one of the immune checkpoint inhibitors (Opdivo, Keytruda, or Tecentriq) may be used if not already given.

The American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines (2017) for systemic therapy for Stage IV NSCLC recommendations regarding immune checkpoint therapy are as follows.²² In patients with either non-squamous cell or squamous cell carcinoma without a tumor *EGFR*-sensitizing mutation or *ALK* or *ROS1* gene rearrangement and with a performance status of 0 or 1 (and appropriate performance status of 2), *first-line therapy* with single-agent Keytruda is recommended if the PD-L1 expression TPS is $\geq 50\%$ and there are no contraindications. Other checkpoint inhibitors, combination checkpoint inhibitors, or immune checkpoint therapy with chemotherapy are not recommended for first-line therapy. For second-line therapy, without a tumor *EGFR*-sensitizing mutation or *ALK* or *ROS1* gene rearrangement and with a performance status of 0 or 1 (and appropriate performance status of 2), patients with a high PD-L1 expression (TPS $\geq 1\%$) and no contraindications who received first-line chemotherapy and have not received prior immune therapy, single agent Opdivo, Keytruda, or Tecentriq are recommended. In patients with negative or unknown PD-L1 expression (TPS $< 1\%$) and no contraindications who received first-line chemotherapy, Opdivo, Tecentriq, or combination cytotoxic chemotherapy is recommended. Other checkpoint inhibitors, combination checkpoint inhibitors, or immune checkpoint therapy with chemotherapy are not recommended.

In one Phase III, open-label, international, study (CHECKMATE-017), 272 patients with metastatic squamous cell NSCLC (Stage IIIB or IV) who had disease progression during or after one prior platinum doublet-based chemotherapy regimen were randomized to receive Opdivo or docetaxel.^{1,23} Patients received Opdivo 3 mg/kg (n = 135) every 2 weeks or docetaxel 75 mg/m² (n = 137) every 3 weeks. The study was terminated early on the basis of a prespecified interim analysis showing that overall survival among patients receiving Opdivo was superior to that among patients taking docetaxel. Planned enrollment was complete before the study was stopped. **Results.** Median overall survival, the primary endpoint, was 9.2 months (95% CI: 7.3, 13.3) with Opdivo and 6.0 months (95% CI: 5.1, 7.3) with docetaxel. The risk of death was 41% lower with Opdivo than with docetaxel (HR 0.59; 95% CI: 0.44, 0.79; P < 0.001). At 1 year, the overall survival rate was 42% (95% CI: 34%, 50%) with Opdivo vs. 24% (95% CI: 17%, 31%) with docetaxel. The ORR was 20% (95% CI: 14%, 28%) with Opdivo and 9% with docetaxel (95% CI: 5%, 15%) [P = 0.008]. Median PFS was 3.5 months (95% CI: 2.1, 4.9) with Opdivo vs. 2.8 months (95% CI: 2.1, 3.5) with docetaxel (HR for death or disease progression was 0.62; 95% CI: 0.47, 0.81; P < 0.001).

A Phase III study open-label study (CHECKMATE-057) compared Opdivo and docetaxel in patients with non-squamous NSCLC that had progressed during or after platinum-based doublet chemotherapy.^{1,24} Patients were treated with Opdivo 3 mg/kg every 2 weeks (n = 287) or with docetaxel 75 mg/m² (n = 268) every 3 weeks. **Results.** At the prespecified interim analysis, median overall survival was 12.2 months (95% CI: 9.7, 15.0) with Opdivo vs. 9.4 months (95% CI: 8.0, 10.7) with docetaxel (HR 0.73; 95% CI: 0.60, 0.89; P = 0.0015). The overall survival rate at 1 year was 51% with Opdivo vs. 39% with docetaxel.²⁴

Two-year outcomes from CHECKMATE-017 and -057 have been reported.²⁵ Minimum follow-up for survival was 24.2 months. In squamous NSCLC, 2-year survival rates with Opdivo vs. docetaxel were 23% (95% CI: 16%, 30%) vs. 8% (95% CI: 4%, 13%) and in non-squamous NSCLC were 29% (95% CI: 24%, 34%) vs. 16% (95% CI: 12%, 20%). Durable responses were observed with Opdivo; 37% of confirmed responders with squamous NSCLC and 34% with non-squamous NSCLC had ongoing

responses after a minimum follow-up of 2 years. No patients in the docetaxel groups had an ongoing response. Treatment-related AEs were lower with Opdivo than with docetaxel.

In one open-label Phase III trial (CHECKMATE-026), Opdivo was compared with chemotherapy in patients with untreated stage IV or recurrent NSCLC and a programmed death ligand 1 (PD-L1) tumor-expression level of $\geq 1\%$.²⁶ Patients were randomized to receive Opdivo 3 mg/kg once every 2 weeks or platinum-based chemotherapy given once every 3 weeks for up to six cycles). Patients receiving chemotherapy could cross over to receive Opdivo at the time of disease progression. The primary end point was PFS, assessed by blinded independent central review, in patients with a PD-L1 expression level of $\geq 5\%$. In the 423 patients with a PD-L1 expression level of $\geq 5\%$, the median PFS survival was 4.2 months with Opdivo vs. 5.9 months with chemotherapy (HR for disease progression or death, 1.15; 95% CI: 0.91, 1.45; P = 0.25). Median overall survival was 14.4 months vs. 13.2 months (HR for death, 1.02; 95% CI: 0.80, 1.30). In all, 60% of patients (n = 128/212) in the chemotherapy group received Opdivo as subsequent therapy. Treatment-related Grade 3 or 4 AEs occurred in 18% of the patients who received Opdivo and in 51% of those who received chemotherapy.

Dosing in Metastatic NSCLC in Adults.

Dosing must meet ONE of the following (A OR B):¹

- a. As a single agent, 240 mg as an intravenous infusion over 30 minutes once every 2 weeks;
- b. As a single agent, 480 mg as an intravenous infusion over 30 minutes once every 4 weeks.

The recommended dose is 240 mg given as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity.¹ Management of AEs may require that Opdivo be withheld or permanently discontinued as determined by the prescribing physician.

Initial Approval/Extended Approval.

- A) *Initial Approval:* Approve for 6 months.
- B) *Extended Approval:* Approve at 6-month intervals if the patient 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.

Labs/Diagnostics. Detection of *EGFR* mutations and *ALK* fusions is necessary for selection of patients appropriate for targeted therapies prior to using Opdivo therapy. This only applies to patients initiating therapy with Opdivo. See criteria above.

7. Renal Cell Carcinoma.

Criteria. The patient must meet the following criteria (A, B, C, and D):

- A) Opdivo is prescribed by or in consultation with an oncologist; AND
- B) The patient has advanced (i.e., relapsed or Stage IV and surgically unresectable) renal cell carcinoma (RCC); AND
- C) The patient meets ONE of the following criteria (i or ii):

- i. The patient has RCC with predominant clear-cell histology and ONE of the following applies (a or b):
 - a) Opdivo will be used as first-line therapy in combination with Yervoy (ipilimumab intravenous injection); OR
 - b) Opdivo will be used as a single agent therapy or in combination with Yervoy AND has tried one of Sutent® (sunitinib malate), Inlyta® (axitinib), Votrient® (pazopanib), Cabometyx® (cabozantinib), or Nexavar® (sorafenib tablets);

The patient has RCC with non-clear cell histology and will use Opdivo as a single agent. Opdivo is indicated for the treatment of patients with advanced RCC who have received prior antiangiogenic therapy.¹

The NCCN guidelines for kidney cancer (version 4.2018) recommend Opdivo as a single-agent therapy for relapse or surgically unresectable Stage IV disease

- as preferred subsequent therapy for predominant *clear-cell* histology (category 1); or
- as systemic therapy for *non-clear cell* histology (category 2A).²⁷

Opdivo is also recommended in combination with Yervoy for relapse or surgically unresectable Stage IV disease

- as preferred first-line therapy for predominant *clear-cell* histology (category 1 for intermediate- or poor-risk group of patients; category 2B for favorable risk group); or
- as subsequent therapy for predominant *clear-cell* histology (category 2A).

The guideline recommendations for *first-line oral therapy* regimens in patients with relapsed or Stage IV and surgically unresectable RCC with predominant *clear-cell* histology include: Sutent (category 1, preferred), Votrient (category 1, preferred), Inlyta (category 2A), and Cabometyx® (cabozantinib tablets) [for poor and intermediate risk groups]. Recommendations for *subsequent therapy* include Cabometyx (category 1, preferred), Opdivo (category 1, preferred), Inlyta (category 1), Lenvima™ (lenvatinib capsules) plus Afinitor® (everolimus tablets) [category 1]; Afinitor, Yervoy plus Opdivo, Sutent, Nexavar, or Votrient are all category 2A recommended therapies. Torisel® (temsirolimus for injection), Avastin® (bevacizumab for injection), and high-dose Proleukin® (aldesleukin for injection, interleukin-2 [IL-2]) for selected patients are all category 2B recommended options.

For patients with *non-clear cell* histology RCC, Sutent and enrollment in clinical trials are noted as preferred therapies (category 2A, preferred); Inlyta, Cabometyx, Afinitor, Lenvima plus Afinitor, Opdivo, Nexavar, Votrient, Avastin, Tarceva® (erlotinib tablets), Avastin plus Tarceva (for selected patients), Avastin plus Afinitor (for selected patients), and Torisel are the other recommended options (all category 2A; Torisel is category 1 for poor prognosis patients).²⁷

Previously treated RCC. In a randomized, open-label, Phase III study (CHECKMATE-025), Opdivo (n = 410) was compared with Afinitor (n = 411) for the treatment of patients with advanced clear-cell RCC.^{1,28} All patients had previously been treated with one or two prior anti-angiogenic regimens of therapy (Sutent 59%, Votrient 30%, Inlyta 12%). Patients were stratified by number of previous regimens received (one or two). The dose of Opdivo was 3 mg/kg every 2 weeks. Patients assigned to Afinitor received 10 mg orally once daily. Dose modifications were allowed only in the Afinitor group. **Results.**

At a pre-planned interim analysis when 398 deaths were observed, median overall survival was 25.0 months (95% CI: 21.7, not estimable) with Opdivo vs. 19.6 months (95% CI: 17.6, 23.1) with Afinitor. Death occurred in 45% of patients assigned to Opdivo vs. 52% of patients assigned to Afinitor (HR for death, 0.73 [95% CI: 0.60, 0.89]; $P = 0.002$) which met the prespecified criteria for superiority. The ORR was 25% with Opdivo vs. 5% with Afinitor (odds ratio, 5.98 [$P < 0.001$]).²⁸ Median time to response was 3.5 months and 3.7 months with Opdivo and Afinitor, respectively. Median PFS was 4.6 months with Opdivo vs. 4.4 months with Afinitor. In subgroup analysis, the HR for death was 0.71 (95% CI: 0.56, 0.90) favoring Opdivo in patients who had one previous anti-angiogenic therapy. In patients who had tried two previous anti-angiogenic therapies, the HR for death was 0.89 (95% CI: 0.61, 1.29) favoring Opdivo. At each assessment through Week 102, changes in quality of life were better with Opdivo than with Afinitor ($P < 0.05$ at each assessment).

Previously untreated RCC. In an open-label, Phase III study (CheckMate-214), adults with advanced, previously untreated *clear-cell* RCC were randomized to receive Opdivo 3 mg/kg plus Yervoy 1 mg/kg intravenously every 3 weeks for four doses ($n = 550$), followed by Opdivo 3 mg/kg every 2 weeks or to Sutent 50 mg once daily for 4 weeks followed by 2 weeks off of each 6-week cycle ($n = 546$).^{1,10} The co-primary endpoint points were overall survival, ORR, and PFS in patients with intermediate or poor prognostic risk. Of the patients assigned to Opdivo plus Yervoy or Sutent, 425 and 422, respectively had intermediate or poor risk. With a median follow-up of 25.2 months in the intermediate- and poor-risk patients, the 18-month overall survival rate was 75% (95% CI: 70%, 78%) with Opdivo plus Yervoy and 60% (95% CI: 55%, 65%) with Sutent. The median overall survival was not reached with Opdivo plus Yervoy and was 26.0 months with Sutent (HR for death, 0.63; $P < 0.002$). The ORR was 42% (Opdivo/Yervoy) vs. 27% (Sutent) and the CR rate was 9% vs. 1%. Median PFS was 11.6 months and 8.4 months, respectively (HR for disease progression or death, 0.82; $P = 0.03$ that was not significant per the prespecified threshold). Grade 3 or 4 AEs occurred in 46% of patients ($n = 250/547$) and 63% of patients ($n = 335/535$), respectively. An exploratory analysis of the 249 favorable risk patients showed a 12-month overall survival rate was 94% with Opdivo plus Yervoy vs. 96% with Sutent and an 18-month overall survival rate of 88% and 93% respectively. Efficacy of Opdivo plus Yervoy in previously untreated RCC with favorable risk disease has not been established.

Dosing in Advanced Renal Cell Carcinoma in Adults. *Dosing must meet the following (A, B, OR C):*

- A)** As a single agent, 240 mg every 2 weeks as an intravenous infusion over 30 minutes; OR
- B)** As a single agent, 480 mg every 4 weeks as an intravenous infusion over 30 minutes; OR
- C)** When used in combination with Yervoy, Opdivo 3 mg per kg once every 3 weeks as an intravenous infusion over 30 minutes for up to 4 doses.

The recommended dose as a single agent is 240 mg given every 2 weeks or 480 mg every 4 weeks as an intravenous infusion over 30 minutes until disease progression or unacceptable toxicity.¹ When Opdivo is used in combination with Yervoy for advanced RCC, the recommended dose is 3 mg/kg every 3 weeks for 4 doses, then 240 mg once every 2 weeks or 480 mg every 4 weeks as a single agent until disease progression or unacceptable toxicity. Management of AEs may require that Opdivo be withheld or permanently discontinued as determined by the prescribing physician.

Initial Approval/Extended Approval.

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

Duration of Therapy in Renal Cell Carcinoma. Indefinite if the patient is responding to therapy.

Labs/Diagnostics. None required.

8. Urothelial Carcinoma.

Criteria. *The patient must meet the following criteria (A, B, C, and D):*

- A) Opdivo is prescribed by or in consultation with an oncologist; AND
- B) The patient has recurrent, locally advanced, or metastatic urothelial carcinoma; AND
- C) Opdivo will be used as a single agent;

- D) The patient has disease progression during or after trying platinum- (cisplatin, carboplatin) containing chemotherapy.

Opdivo is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.¹ This indication is approved under accelerated approval based on tumor response rate and duration of response.

The NCCN guidelines on bladder cancer (version 3.2018) recommend Opdivo as a single agent for urothelial carcinoma of the *bladder* for clinical stage T4b or T2-T4a, N1-3 disease, or for recurrence post cystectomy, or for metastatic disease as subsequent systemic therapy post-platinum (alternative preferred) [category 2A].^{29,50} Opdivo is also recommended as a single agent for urothelial carcinoma as subsequent systemic therapy post-platinum for primary carcinoma of the urethra (recurrent or metastatic disease), upper genitourinary tract tumors (metastatic disease), and urothelial carcinoma of the prostate (metastatic disease) [all category 2A].

The efficacy of Opdivo was established in one multicenter, Phase II trial (CHECKMATE-275) in patients with metastatic or surgically unresectable locally advanced urothelial carcinoma whose disease had progressed or recurred after previous therapy with at least one platinum-based chemotherapy regimen.^{1,30} Patients received Opdivo 3 mg/kg intravenously every 2 weeks until disease progression and clinical deterioration, unacceptable toxicity, or other defined reasons. The primary endpoint was ORR confirmed by blinded independent review committee in all treated patients and by tumor PD-L1 expression of $\geq 5\%$ and $\geq 1\%$. In all, 265 patients were evaluated for efficacy. The ORR was 19.6% of patients (n = 52/265; 95% CI: 15.0%, 24.9%); 6 patients had a CR and 46 patients had a PR.³⁰ The ORR was 28.4% of patients (n = 23/81; 95% CI: 18.9%, 39.5%) with PD-L1 expression $\geq 5\%$; 23.8% of patients (n = 29/122; 95% CI: 16.5%, 32.3%) with PD-L1 expression $\geq 1\%$; and 16.1% of patients (n = 23/143; 95% CI: 10.5%, 23.1%) with PD-L1 expression $< 1\%$. Median duration of response was 10.3 months in all 270

patients; 7.6 months in patients with PD-L1 expression < 1%; and not estimable in patients with PD-L1 expression ≥ 1%.¹

Dosing in Urothelial Carcinoma in Adults.

. Dosing must meet ONE of the following(A OR B):

- a. As a single agent, 240 mg as an intravenous infusion over 30 minutes once every 2 weeks; OR
- b. As a single agent, 480 mg as an intravenous infusion over 30 minutes once every 4 weeks.

The recommended dose of Opdivo is 240 mg every 2 weeks or 480 mg every 4 weeks as an intravenous infusion over 30 minutes until disease progression or unacceptable toxicity.¹

Management of AEs may require that Opdivo be withheld or permanently discontinued as determined by the prescribing physician.

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 Urothelial Carcinoma in Adults. Indefinite if the patient is responding to therapy.

Labs/Diagnostics. None required.

Other Uses With Supportive Evidence

9. Anal Carcinoma.

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

- A) Opdivo is prescribed by or in consultation with an oncologist; AND
- B) The patient has metastatic squamous cell anal carcinoma;⁴⁸ AND
- C) The patient has received other chemotherapy (e.g., 5-fluorouracil [5-FU] plus cisplatin, carboplatin plus paclitaxel, FOLFOX [oxaliplatin, leucovorin, and 5-FU]); AND
- D) Opdivo will be used as a single agent.

The NCCN guidelines on anal carcinoma (version 2.2018) recommend Opdivo for squamous cell anal carcinoma as second-line (subsequent) therapy as a single agent for metastatic disease (category 2A).⁴⁸ Primary treatment for metastatic disease includes 5-FU/cisplatin ± radiation therapy (RT), carboplatin/paclitaxel ± RT, or FOLFOX ± RT.

In one Phase II single-arm, multicenter trial, 37 patients with treatment refractory metastatic squamous cell carcinoma of the anal canal received Opdivo 3 mg/kg every 2 weeks intravenously.⁴⁹ Patients had at least one previous systemic therapy for surgically unresectable or metastatic disease. Median follow-up was 10.1 months. Patients had received at least one dose of Opdivo. Objective responses were achieved in 24% of patients (n = 9/37) with two CRs and seven PRs; 47% of patients (n = 17/37) had stable disease.

Dosing in Anal Carcinoma in Adults. *Dosing must meet ONE of the following (A OR B):*

- a. As a single agent, 240 mg as an intravenous infusion over 30 minutes once every 2 weeks; OR
- b. As a single agent, 3 mg per kg as an intravenous infusion over 30 minutes once every 2 weeks.

The NCCN guidelines on anal carcinoma recommend a dose of Opdivo 240 mg every 2 weeks or 3 mg/kg every 2 weeks for subsequent therapy of metastatic anal carcinoma.⁴⁸

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 Anal Carcinoma in Adults. Indefinite if the patient is responding to therapy.

Labs/Diagnostics. None required.

10. Brain Metastases Due to Melanoma.

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. One of the following applies (i or ii):
 - i. The patient has recurrent disease and Opdivo is active against the primary melanoma tumor;³¹ OR
 - ii. The patient has newly diagnosed asymptomatic brain metastases; AND
- B) AND
- C) Opdivo will be used in combination with Yervoy (ipilimumab injection).³¹

The NCCN guidelines on central nervous system cancers (version 1.2018) recommend Opdivo be used in combination with Yervoy as treatment for limited brain metastases in patients with melanoma for newly diagnosed brain metastases in select patients (e.g., patients with small asymptomatic brain metastases) with newly diagnosed or stable systemic disease or reasonable systemic treatment options OR for recurrent brain metastases (category 2A).³¹ Opdivo is also recommended in combination with Yervoy for treatment of extensive brain metastases for recurrent disease in patients with melanoma and stable systemic disease or reasonable systemic treatment options (category 2A).

In a multicenter trial (CHECKMATE-204), patients with ≥ 1 measurable brain metastases and no neurologic symptoms, received Opdivo 1 mg/kg plus Yervoy 3 mg/kg every 3 weeks for four doses, and then Opdivo 3 mg/kg every 2 weeks until progression or toxicity.³² The primary endpoint was intracranial clinical benefit rate (CR + PR + SD for > 6 months). Ninety patients have been accrued and this report includes 75 patients with disease assessment before the database lock. In all, 26 patients received four Opdivo plus Yervoy doses and 51% of patients (n = 38/75) began Opdivo maintenance. The intracranial ORR was 56% (95% CI: 44%, 68%); 19% of patients had a CR. Treatment-related Grade 3 or 4 AEs occurred in 48% of patients.

In a randomized Phase II trial, patients with asymptomatic brain metastases with no prior local brain therapy were randomized to Cohort A (Opdivo 1 mg/kg plus Yervoy 3 mg/kg every 3 weeks for four doses, and then Opdivo 3 mg/kg every 2 weeks), Cohort B (Opdivo 3 mg/kg every 2 weeks), or Cohort C (Opdivo 3 mg/kg every 2 weeks in patients with brain metastases that failed local therapy, were neurologically symptomatic and/or with leptomeningeal disease).³³ Prior BRAF inhibitor therapy was allowed. The primary endpoint was the best intracranial response (ICR) \geq Week 12. A total of 66 patients with median follow-up of 14 months were included in the analysis. In Cohort A (n = 25), the ICR was 44% (95% CI: 24%, 65%) and in Cohort B (n = 25) the ICR was 20% (95% CI: 7%, 41%). Patients with symptomatic brain metastases, leptomeningeal metastases, or previous local therapy responded poorly to Opdivo alone.

Dosing in Brain Metastases Due to Melanoma in Adults. *Dosing must meet the following:* As combination therapy with Yervoy, the initial dose of Opdivo is 1 mg per kg as an intravenous infusion over 60 minutes once every 3 weeks for four doses and then followed by 3 mg per kg every 2 weeks.³²⁻³³

Opdivo 3 mg per kg as an intravenous infusion over 60 minutes once every 2 weeks has been used as single-agent therapy.³³

Initial Approval/Extended Approval.

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

Duration of Therapy in Brain Metastases Due to Melanoma. Indefinite if the patient is responding to therapy.

Labs/Diagnostics. None required.

11. Malignant Pleural Mesothelioma.

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 unresectable malignant pleural mesothelioma; AND
- c. The patient has tried first-line chemotherapy (e.g., Alimta [pemetrexed] plus cisplatin or carboplatin, Alimta [pemetrexed] with cisplatin and Avastin [bevacizumab], gemcitabine plus cisplatin, Alimta alone, vinorelbine).

The NCCN guidelines on malignant pleural mesothelioma (version 2.2018) recommend Opdivo as subsequent systemic therapy as a single agent or in combination with Yervoy (category 2B).³⁴ The NCCN Panel recommendation is based on the toxicities of the regimen. Single-agent therapy with Keytruda, vinorelbine, or gemcitabine are recommended for subsequent therapy (category 2A). Therapy with Alimta is an option if not given first line (category 1).

In one Phase II, multicenter trial conducted in France, adults (n = 108) with malignant pleural mesothelioma that had relapsed after 1 or 2 prior lines of therapy including Alimta with a platinum agent were randomized to receive Opdivo 3 mg/kg every 2 weeks or to Opdivo 3 mg/kg every 2 weeks plus Yervoy 1 mg/kg every 6 weeks.³⁵ Therapy continued until progression or unacceptable toxicity. The primary endpoint was the disease control rate (DCR) at 12 weeks using a blinded independent central review committee for assessment. In all, 125 patients were enrolled with a median age of 71.8 years (range, 32.5 to 88.1 years); 69.6% of patients had one previous line of therapy. Also, 70% of the patients received ≥ 3 cycles of either treatment. At 12 weeks, the DCR in the first 108 patient was 42.6% (95% CI: 29.4%, 55.8%) with Opdivo and 51.9% (95% CI: 38.5%, 65.2%) with Opdivo plus Yervoy. The ORR was 16.7% (95% CI: 6.7%, 26.6%) with Opdivo and 25.9% (95% CI: 14.2%, 37.6%) with Opdivo plus Yervoy. All Grade 3 or 4 toxicities were slightly increased in the combination arm (86.9% and 16.4%, respectively) vs. Opdivo alone (77.8% and 9.5%, respectively). Three treatment-related deaths were occurred in the combination arm.

Dosing in Malignant Pleural Mesothelioma in Adults. *Dosing must meet the following:* As a single agent or in combination with Yervoy, 3 mg per kg as an intravenous infusion over 60 minutes once every 2 weeks.³⁵

Initial Approval/Extended Approval.

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

Duration of Therapy in Malignant Pleural Mesothelioma. Indefinite if the patient is responding to therapy.

Labs/Diagnostics. None required.

12. **Melanoma, Uveal.**

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 metastatic or unresectable uveal melanoma.⁴⁴

The NCCN guidelines on uveal melanoma (version 1.2018) recommend Opdivo be considered for metastatic or unresectable disease as a single agent or in combination with Yervoy (category 2A).⁴⁴ Enrollment in a clinical trial is preferred. Uveal melanoma is sensitive to some of the same systemic therapies used to treat cutaneous melanoma. Response rates are lower with uveal melanoma than with cutaneous melanoma, but individual patients may sometimes derive substantial benefit. Examples of other systemic agents that may be effective include Keytruda, Yervoy, dacarbazine, temozolomide, paclitaxel, Abraxane, carboplatin plus paclitaxel, and Mekinist® (trametinib tablets).

In a Phase II multicenter, single arm, open-label study (GEM1402) conducted in Spain, Opdivo in combination with Yervoy was used as first-line therapy in 19 adult patients with metastatic uveal

melanoma.⁴⁵ Treatment was Opdivo 1 mg/kg every 3 weeks and four doses of Yervoy 3 mg/kg every 3 weeks (cycles 1 and 2), followed by Opdivo 3 mg/kg every 2 weeks until disease progression, toxicity or withdrawal. In all, 11 patients completed cycle 2 and 8 patients stopped after one dose. An interim analysis showed an ORR of 15.8% and 47.4% of patients had stable disease. With a median follow-up 4.6 months, PFS was 4.99 months. This trial is ongoing.

Results from a series of 56 patients with Stage IV uveal melanoma treated with Opdivo, Keytruda, or Tecentriq at eight institutions in the US and one in Spain were reported.⁴⁶ Patients had baseline imaging and follow-up data. In all, 62.5% of the patients had previously received Yervoy. Many of the patients received doses and treatment schedules of Keytruda or Opdivo that differed from the FDA approved doses. There were two patients with a PR and five patients with stable disease for at least 6 months.

In one retrospective analysis, patients with metastatic uveal melanoma had received therapy with either Opdivo 3 mg/kg every 2 weeks or Keytruda 2 mg/kg every 3 weeks as monotherapy or combined therapy with either Opdivo or Keytruda plus Yervoy.⁴⁷ The combination regimens with Yervoy were as follows: Yervoy 3 mg/kg plus Opdivo 1 mg/kg every 3 weeks followed by Opdivo 3 mg/kg every 2 weeks; Yervoy 1 mg/kg plus Opdivo 3 mg/kg every 3 weeks followed by Opdivo 3 mg/kg every 2 weeks; and Yervoy 1 mg/kg plus Keytruda 2 mg/kg every 3 weeks followed by Keytruda 2 mg/kg every 3 weeks. Patients were treated in 20 German skin cancer centers and had an evaluable disease course with follow-up of ≥ 3 months. Eighty-six (86) patients received monotherapy (Opdivo, n = 32; Keytruda, n = 54) and 15 patients received combined therapy. The response rate with monotherapy was 4.7% and median overall survival was 10 months with Opdivo and 14 months with Keytruda. PRs were reported in two patients receiving combination therapy.

Dosing in Uveal Melanoma in Adults. *Dosing must meet the following (A, B, OR C):*

- a. As a single agent, 3 mg per kg as an intravenous infusion once every 2 weeks;^{45,47} OR
- b. When used in combination with Yervoy, Opdivo 1 mg per kg once every 3 weeks as an intravenous infusion over 30 minutes for up to 4 doses;^{45,47}
- c. Other dosing regimens will be reviewed on a case-by-case basis.

Opdivo or Opdivo plus Yervoy is not an FDA-approved use in uveal melanoma. Limited information is available on dosing for uveal melanoma. Dosing information in patients with uveal melanoma is described above. The NCCN guidelines recommend monotherapy or combination therapy with Yervoy, but do not include dosing recommendations. Management of AEs may require that Opdivo be withheld or permanently discontinued as determined by the prescribing physician.¹

Initial Approval/Extended Approval.

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

Duration of Therapy in Uveal Melanoma. Indefinite if the patient is responding to therapy.

Labs/Diagnostics. None required.

13. Merkel Cell Carcinoma.

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

- C) Opdivo is prescribed by or in consultation with an oncologist; AND
- D) The patient has disseminated Merkel cell carcinoma.³⁶

The NCCN guidelines on Merkel cell carcinoma (version 1.2018) recommend Opdivo for treatment of disseminated, clinical M1 disease with or without surgery and/or radiation therapy (category 2A).³⁶ Enrollment in a clinical trial is preferred. Preliminary data from non-randomized trials in patients with Merkel cell carcinoma show that rates of durable response are improved with PD-1/PD-L1 blockade compared with cytotoxic therapy.

Dosing in Merkel Cell Carcinoma in Adults.

Dosing must meet the following: As a single agent, 3 mg per kg as an intravenous infusion over 60 minutes once every 2 weeks.³⁸⁻³⁹

Opdivo is not an FDA approved use in Merkel cell carcinoma. Very limited information is available on use of Opdivo. Dosing in case reports was 3 mg/kg once every 2 weeks.³⁸⁻³⁹ Management of AEs may require that Opdivo be withheld or permanently discontinued as determined by the prescribing physician.¹

Initial Approval/Extended Approval.

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

Duration of Therapy in Merkel Cell Carcinoma. Indefinite if the patient is responding to therapy.

Labs/Diagnostics. None required.

14. Small Cell Lung Cancer (SCLC).

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 relapsed or progressed after receiving a platinum- (cisplatin, carboplatin) containing chemotherapy.

The NCCN guidelines on small cell lung cancer (version 2.2018) recommend Opdivo as subsequent systemic therapy for patients with performance status 0 to 2 as a single agent or in combination with Yervoy 1) for relapse within 6 months following CR or PR or stable disease with initial treatment, or 2) for primary progressive disease.⁴⁰ Enrollment in a clinical trial is strongly encouraged and preferred. Patients who relapse > 6 months after initial treatment are treated with

their original regimen. Initial systemic therapy for limited stage or extensive stage disease includes cisplatin- or carboplatin-based regimens.

In one Phase I/II, multicenter, open-label trial (CHECKMATE-032) a cohort of patients with SCLC received Opdivo or Opdivo plus Yervoy.⁴¹ Patients were ≥ 18 years of age, had limited stage or extensive stage SCLC, and had progressed after at least one platinum-containing regimen. Patients received Opdivo 3 mg/kg intravenously every 2 weeks until disease progression or unacceptable toxicity or Opdivo plus Yervoy. The combination regimens were as follows: Opdivo 1 mg/kg plus Yervoy 1 mg/kg, Opdivo 1 mg/kg plus Yervoy 3 mg/kg, or Opdivo 3 mg/kg plus Yervoy 1 mg/kg given every 3 weeks for four cycles and then followed by Opdivo 3 mg/kg every 2 weeks. Patients in the Opdivo plus Yervoy arm were assessed in a dose-escalating safety phase for the combination beginning at Opdivo 1 mg/kg plus Yervoy 1 mg/kg. Depending on tolerability, patients were then assigned to Opdivo 1 mg/kg plus Yervoy 3 mg/kg or Opdivo 3 mg/kg plus Yervoy 1 mg/kg. The primary endpoint was ORR by investigator assessment. This trial is ongoing and the published trial is an interim analysis of the SCLC cohort. Between November 18, 2013, and July 28, 2015, 216 patients were enrolled and treated with Opdivo 3 mg/kg (n = 98), with Opdivo 1 mg/kg plus Yervoy 1 mg/kg (n = 3), with Opdivo 1 mg/kg plus Yervoy 3 mg/kg (n = 61), and with Opdivo 3 mg/kg plus Yervoy 1 mg/kg (n = 54). At database lock on November 6, 2015, median follow-up for patients continuing in the study (including those who had died or discontinued treatment) was 198.5 days (interquartile range [IQR], 163.0 to 464.0 days) for Opdivo 3 mg/kg, 302 days (IQR not calculable) for Opdivo 1 mg/kg plus Yervoy 1 mg/kg, 361.0 days (IQR, 273.0 to 470.0 days) for Opdivo 1 mg/kg plus Yervoy 3 mg/kg, and 260.5 days (IQR 248.0 to 288.0 days) for Opdivo 3 mg/kg plus Yervoy 1 mg/kg.

Results. An ORR was attained in 10% of patients (n = 10/98) with Opdivo 3 mg/kg; 33% (n = 1/3) receiving Opdivo 1 mg/kg plus Yervoy 1 mg/kg; 23% (n = 14/61) receiving Opdivo 1 mg/kg plus Yervoy 3 mg/kg; and 19% (n = 10/54) receiving Opdivo 3 mg/kg plus Yervoy 1 mg/kg. Grade 3 or 4 treatment-related AEs occurred in 13% patients in the Opdivo 3 mg/kg cohort, 30% in the Opdivo 1 mg/kg plus Yervoy 3 mg/kg cohort, and 19% in the Opdivo 3 mg/kg plus Yervoy 1 mg/kg cohort; the most commonly reported Grade 3 or 4 treatment-related AEs were increased lipase and diarrhea. No patients in the Opdivo 1 mg/kg plus Yervoy 1 mg/kg cohort had a Grade 3 or 4 treatment-related AE. Two patients who received Opdivo 1 mg/kg plus Yervoy 3 mg/kg died from treatment-related AEs (myasthenia gravis and worsening of renal failure), and one patient who received Opdivo 3 mg/kg plus Yervoy 1 mg/kg died from treatment-related pneumonitis. Updated results from the initial (non-randomized) Opdivo and Opdivo 1 mg/kg plus Yervoy 3 mg/kg arms showed ORRs of 11% and 25%, respectively.⁴²

This trial has added a randomized expansion cohort where 247 patients were randomized to Opdivo 3 mg/kg every 2 weeks or Opdivo 1 mg/kg plus Yervoy 3 mg/kg every 3 weeks for four cycles followed by Opdivo 3 mg/kg every 2 weeks.⁴³ An exploratory analysis of the SCLC cohort (pooled nonrandomized and randomized patients in CheckMate-032; n = 401), was reported based on a data base lock on March 30, 2017. This analysis of the 211 patients evaluable for efficacy analyses by tumor mutational burden showed that efficacy was increased in SCLC that had high tumor mutational burden. ORRs with Opdivo alone vs. Opdivo plus Yervoy were higher in patients with high tumor mutational burden (i.e., 21.3% vs. 46.2%, respectively) than in patients with low (4.8% vs. 22.2%, respectively) or medium (6.8% vs. 16.0%, respectively) tumor mutational burden.

Dosing in SCLC in Adults. *Dosing must meet ONE of the following (A OR B):*

PM119_CCC_Nivolumab_(Opdivo)

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- A) As a single agent, 3 mg/kg as an intravenous infusion over 60 minutes once every 2 weeks; OR
- B) If used in combination with Yervoy (for SCLC), one of the following (i or ii):⁴¹
 - i. 1 mg/kg once every 3 weeks for 4 doses if used with Yervoy 1 mg/kg or Yervoy 3 mg/kg, then followed by Opdivo 3 mg/kg once every 2 weeks; OR
 - ii. 3 mg/kg once every 3 weeks for 4 doses if used with Yervoy 1 mg/kg, then followed by Opdivo 3 mg/kg once every 2 weeks.

Opdivo or Opdivo plus Yervoy is not an FDA approved use in SCLC. Dosing in the Phase II trial in patients with SCLC⁴¹ is described above. Management of AEs may require that Opdivo be withheld or permanently discontinued as determined by the prescribing physician.

Initial Approval/Extended Approval.

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

Duration of Therapy in SCLC. Indefinite if the patient is responding to therapy.

Labs/Diagnostics. None required.

13. 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.

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

Waste Management for All Indications.

The dose should be calculated and the number of vials needed assessed. Dosing for Opdivo as a single agent in patients with melanoma, NSCLC, RCC, cHL, SCCHN, urothelial carcinoma, and HCC is 240 mg or 480 mg. In CRC, Opdivo dosing as a single agent is 240 mg. When used in combination with Yervoy for melanoma or RCC, the dose of Opdivo is based on body weight (mg/kg). For Other Uses with Supportive Evidence, the dose is usually in mg/kg of body weight. The number of vials needed should be calculated and the entire vials are used. For other uses, see the dosing sections.

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. (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.

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CFR	
WAC	
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Contract Citation	<input type="checkbox"/> WAH <input type="checkbox"/> IMC <input type="checkbox"/> MA
Other Requirements	
NCQA Elements	

Revision History

Revision Date	Revision Description	Revision Made By
12/23/2015	New	Kelly Force; Yusuf Rashid, RPh
12/24/2015	Approval	MMLT
01/11/2017	No revisions	Fran McGaugh
01/12/2017	Approval	MMLT
07/20/2017	Criteria completely updated and revised	Michael Sporck, Pharmacy Intern Sophia Yun, PharmD
07/25/2017	Approved	MMLT
05/17/2018	Revised	Jennifer Farley, PharmD
06/11/2018	Reassigned from UM 129, transferred to new template	Cindy Bush
06/14/2018	Approval	UM Committee
07/12/2018	Revised	Jennifer Farley, PharmD
09/19/2018	Approval	UM Committee