Department:	Pharmacy Management	**Original Approval:**	12/24/2015
Policy #:	PM117	**Last Approval:**	09/19/2018
Title:	Pembrolizumab (Keytruda®)		
Approved By:	UM Committee		

REQUIRED CLINICAL DOCUMENTATION FOR REVIEW

Documentation required to determine medical necessity for Pembrolizumab (Keytruda): History and/or physical examination notes and relevant specialty consultation notes that address the problem and need for the service: -Diagnosis -Age -Medication list (current and past) including all biologic agents -Labs/diagnostics.

BACKGROUND

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

1) For the treatment of patients with unresectable or metastatic melanoma; AND
2) As a single agent for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have high programmed death-ligand 1 (PD-L1) expression (tumor proportion score [TPS] ≥ 50%) as determined by an FDA-approved test, with no epidermal growth factor receptor (*EGFR*) or anaplastic lymphoma kinase (*ALK*) genomic tumor aberrations; AND
3) As a single agent for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥ 1%) as determined by an FDA-approved test and with disease progression on or after platinum-containing chemotherapy. Patients with *EGFR* or *ALK* genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Keytruda; AND
4) In combination with Alimta® (pemetrexed intravenous injection) and carboplatin for the first-line treatment of patients with metastatic non-squamous NSCLC. This indication is approved under accelerated approval based on tumor response rate and progression-free survival (PFS). Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.
5) Treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy.*
6) Treatment of adult and pediatric patients with refractory classical Hodgkin lymphoma (cHL), or who have relapsed after three or more prior lines of therapy.*
7) Treatment of adult and pediatric patients with refractory primary mediastinal large B-cell lymphoma (PMBCL), or who have relapsed after two or more prior line of therapy;* AND
   Limitation of Use: Keytruda is not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy.
8) Treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (Combined Positive Score [CPS] ≥ 10),

or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status;* OR

Treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy; AND

9) Treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, OR for colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.* *Limitation of Use:* The safety and effectiveness of Keytruda in pediatric patients with MSI-H central nervous system cancers have not been established.
10) Treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1 (Combined Positive Score [CPS] ≥ 1) as determined by an FDA-approved test, with disease progression on or after two or more lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, human epidermal growth factor receptor 2 (HER2)/neu-targeted therapy.*
11) Treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA-approved test.*

*This indication is 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.

For pediatric patients with cHL or children with MSI-H, the recommended dose of Keytruda is 2 mg/kg (up to a maximum of 200 mg) as an intravenous infusion over 30 minutes every 3 weeks.[1] For melanoma, HNSCC, NSCLC, cHL (adults), PMBCL (adults), urothelial carcinoma, or MSI-H/dMMR solid tumors (adults), gastric or GEJ adenocarcinoma, or cervical cancer, the dose is 200 mg as an intravenous infusion over 30 minutes every 3 weeks. Keytruda is available as a 50 mg lyophilized powder in a single-use vial for reconstitution and as a 100 mg/4 mL solution in a single-use vial. The lyophilized powder is reconstituted with 2.3 mL of Sterile Water for Injection (resulting concentration 25 mg/mL). The solution or reconstituted powder is diluted with 0.9% Sodium Chloride Injection or 5% Dextrose Injection for intravenous infusion to a final concentration of between 1 mg/mL to 10 mg/mL.

DEFINITIONS

None.

INDICATIONS/CRITERIA

Medicaid Members	***Continue to criteria for approval below.***
Medicare Members	***Step-utilization of Part D drugs not required.***

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

FDA-Approved Indications

1. Cervical Cancer.

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

A) Keytruda is prescribed by or in consultation with an oncologist; AND

B) The patient has recurrent or metastatic cervical cancer;[1] AND

C) The patient has tried chemotherapy (e.g., cisplatin/paclitaxel/Avastin [bevacizumab intravenous injection]; cisplatin/paclitaxel; topotecan/paclitaxel/Avastin; carboplatin/paclitaxel; cisplatin or carboplatin; paclitaxel); AND

D) The patient's tumor expression for programmed death-ligand 1 (PD-L1) as determined by a FDA-approved test has a combined positive score (CPS) ≥ 1;[1] AND

E) Keytruda is being used as single-agent therapy.

Note: Also see **Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors.**

The National Comprehensive Cancer Network (NCCN) guidelines on cervical cancer (version 1.2018) do not include this new FDA approved indication.[46] These guidelines recommend Keytruda as second-line therapy for treatment of patients with recurrent or metastatic MSI-H or dMMR tumors (category 2B). The guidelines recommended that enrollment in a clinical trial be strongly considered. Preferred systemic therapies are chemoradiation with cisplatin alone or cisplatin plus 5-fluorouracil (5-FU). First-line combination therapies for recurrent or metastatic disease include cisplatin/paclitaxel/Avastin; cisplatin/paclitaxel; topotecan/paclitaxel/Avastin; and carboplatin/paclitaxel (in patients who have received prior cisplatin) [all of these are category 1 recommendations]. Regimens with a category 2A recommendation include carboplatin/paclitaxel/Avastin, cisplatin/topotecan, and topotecan/paclitaxel. Other possible first-line single agent therapies are cisplatin (preferred single agent), carboplatin, or paclitaxel. Second-line therapies are listed in the guidelines and are all category 2B recommendations.

In one Phase Ib multicenter, trial that included 20 solid tumor cohorts (Keynote-028), patients with recurrent or metastatic cervical cancer were treated with Keytruda 200 mg intravenously every 3 weeks until unacceptable toxicity or disease progression for up to 24 weeks.[1,47] The objective response rate (ORR) was the primary endpoint assessed by blinded independent central review (BICR) and duration of response. In the 98 patients, 79% (n = 77/98) had tumors that expressed PD-L1 with a CPS ≥ 1 and received at least one line of therapy in the metastatic setting. At baseline, 92% of patients had squamous cell carcinoma, 6% had adenocarcinoma, and 1% adenosquamous histology; 95% of patients had M1 disease and 5% had recurrent disease. In addition, 35% of patients had one and 65% had two or more prior lines of therapy in the recurrent or metastatic setting. ***Results***. No responses were reported in patients whose tumors did not have PD-L1 expression (CPS < 1). In 77 patients with a median follow-up of 11.7 months (range, 0.6 to 22.7 months), the ORR was 14.3% (95% confidence interval [CI]: 7.4%, 24.1%); 2.6 % of patients had a complete response (CR) and 11.7% had a partial response (PR). Median duration of response was

not reached and ranged from 4.1 to 18.6+ months. Results from 24 patients in this trial are published with a median follow-up of 11.0 months,[47] ORR was 17% (95% CI: 5%, 37%).

Dosing in Cervical Cancer in Adults. *Dosing must meet the following*: As a single agent, 200 mg as an intravenous infusion over 30 minutes every 3 weeks.[1]

The recommended dose is 200 mg given as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.[1] There are no recommended dose reductions in the prescribing information. Management of AEs may require that Keytruda 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 Cervical Cancer in Adults. Indefinite if the patient has a response or stable disease as determined by the prescribing physician.

Labs/Diagnostics. PD-L1 protein expression in recurrent or metastatic cervical cancer is determined by using CPS, which is the number of PD-L1 staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100. The specimen should be considered to have PD-L1 expression if CPS ≥ 1. Determination of PD-L1 expression using an FDA-approved test (PD-L1 IHC 22C3 pharmDx Kit [Dako]) is required before initiating therapy with Keytruda. The CPS must be ≥ 1 as determined by the PD-L1 test.

2. Classical Hodgkin Lymphoma (cHL).

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

F) Keytruda is prescribed by or in consultation with an oncologist; AND

G) Keytruda is being used as single agent therapy; AND

H) The patient has relapsed or progressive disease;[1] AND ONE the following conditions apply (i, ii, or iii):

- **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[2] according to the prescribing physician.

Keytruda is indicated for the treatment of adult and pediatric patients with refractory cHL, or who have relapsed after 3 or more prior lines of therapy.[1] Efficacy for pediatric patients with cHL is extrapolated from the results in the adult population. This indication is approved under accelerated approval based on tumor response rate and durability of response.

The NCCN clinical practice guidelines on Hodgkin lymphoma (version 3.2018) recommend Keytruda as subsequent systemic therapy as a single agent in patients ≥ 18 years of age with cHL for refractory disease in patients who have relapsed after ≥ 3 prior lines of therapy (category 2A).[2-3] In patients with cHL who are > 60 years of age, single-agent Keytruda is recommended as palliative therapy for refractory disease or in those who have relapsed after ≥ 3 prior lines of therapy (category 2A).[2-3]

As a general guideline, the checkpoint inhibitors (Keytruda or Opdivo® [nivolumab 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.[2] 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, Keytruda, 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.

Children and adolescents usually respond to first-line therapy for cHL and no uniform second-line treatment strategy exists for this patient population.[4] Chemotherapy is the recommended second-line therapy. Agents used alone or in combination regimens for refractory or recurrent Hodgkin lymphoma include the following: ICE (ifosfamide, carboplatin, and etoposide), ifosfamide plus vinorelbine with or without Velcade® (bortezomib intravenous injection), vinorelbine plus gemcitabine, IEP/ABVD/COPP (ifosfamide, etoposide, prednisone/doxorubicin, bleomycin, vinblastine, dacarbazine/cyclophosphamide, vincristine, procarbazine, prednisone), EPIC (etoposide, prednisolone, ifosfamide, plus cisplatin), APE (cytarabine, cisplatin, plus etoposide), MIED (high-dose methotrexate [MTX], ifosfamide, etoposide, plus dexamethasone), Rituxan® (rituximab injection for intravenous [IV] infusion), and Adcetris. Chemotherapy followed by auto-HSCT or allogeneic HSCT are also used.

In one Phase II pivotal study (Keynote-087), Keytruda therapy was evaluated in three cohorts of patients (≥ 18 years of age) with relapsed or refractory cHL as follows: after auto-HSCT and subsequent Adcetris therapy (Cohort 1; n = 69); patients ineligible for auto-HSCT due to chemo-resistance (no response to salvage chemotherapy) and Adcetris therapy failure (Cohort 2; n = 81); and relapsing or refractory cHL after auto-HSCT but not treated with Adcetris after auto-HSCT (Cohort 3; n = 60).[5] Patients received Keytruda 200 mg every 3 weeks. The primary endpoint was ORR by central review, with response assessed every 12 weeks according to Revised Response Criteria for Malignant Lymphomas. Prespecified interim analysis, based on investigator-assessed response, was performed after 30 patients reached first response assessment in all Cohorts. At time

of data cutoff (September 25, 2016), 90 patients had discontinued Keytruda and 120 patients were still receiving Keytruda. Median duration of follow-up was 8.3 months. Patients had received a median of four previous lines of therapy. By design, all of the patients in Cohorts 1 and 2 had failed prior Adcetris therapy. ***Results***. Across all Cohorts, the ORR was 69.0% (95% CI: 62.3%, 75.2%), and the complete response rate (CRR) was 22.4% (95% CI: 16.9%, 28.6%).

In one multicenter, open-label, Phase 1b trial (Keynote-013), patients with relapsed or refractory cHL received therapy with Keytruda.[6] All patients had failed on Adcetris therapy and 67% of patients had failed prior auto-HSCT. In 31 patients who were evaluable for analysis, the ORR was 65% (90% CI: 48%, 79%); five patients attained complete remission, 15 patients had partial remission, and seven patients had stable disease as their best response.

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

- **A)** As a single agent, in adults (≥ 18 years of age), 200 mg as an intravenous infusion over 30 minutes every 3 weeks.[1]
- **B)** As a single agent, in pediatric patients (less than 18 years of age), 2 mg per kg (up to a maximum of 200 mg) given as an intravenous infusion over 30 minutes every 3 weeks.[1]

For cHL the recommended dose of Keytruda in adults is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression. The recommended dose in pediatric patients is 2 mg/kg (up to a maximum of 200 mg), administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

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 cHL. Indefinite if the patient has a response or stable disease as determined by the prescribing physician.

Labs/Diagnostics. None required.

3. Gastric Cancer, Gastroesophageal Junction (GEJ) Cancer, or Esophageal Cancer.

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

- **A)** Keytruda is prescribed by or in consultation with an oncologist; AND
- **B)** The patient has recurrent locally advanced or metastatic disease;[1,28] AND
- **C)** The patient's tumor expression for programmed death-ligand 1 (PD-L1) as determined by a FDA-approved test has a combined positive score (CPS) ≥ 1;[1,28-29] AND
- **D)** The patient has tried therapy with a fluoropyrimidine (e.g., 5-fluorouracil [5-FU], capecitabine) and platinum (e.g., cisplatin, carboplatin); AND

E) If the patient's tumor is human epidermal growth factor receptor 2 (HER2) or HER2/neu positive, targeted therapy with Herceptin® (trastuzumab intravenous infusion) has been tried;[1,28] AND
F) Keytruda will be used as a single agent.[1,28-29]

Note: also see **Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors.**

According to the prescribing information, patients with metastatic gastric cancer are selected for treatment with Keytruda as a single agent based on the presence of positive PD-L1 expression.[1] If PD-L1 expression is not detected in an archival gastric cancer specimen, the feasibility of obtaining a tumor biopsy for PD-L1 testing should be evaluated. PD-L1 expression was evaluated by the PD-L1 IHC 22C3 pharmDx Kit (Dako) and PD-L1 positivity was based on a CPS ≥ 1. CPS is determined by the number of PD-L1 staining cells (tumor cells, lymphocytes, macrophages) divided by total number of tumor cells evaluated, multiplied by 100.

The NCCN guidelines on gastric cancer (version 2.2018)[28] and on esophageal and esophagogastric junction cancers (version 2.2018)[29] recommend Keytruda as palliative therapy for patients who are not surgical candidates or have unresectable locally advanced, recurrent, or metastatic disease and Karnofsky performance status score ≥ 60% or Eastern Cooperative Oncology Group performance score (ECOG PS) ≤ 2 as follows: 1) preferred second-line or subsequent therapy as a single agent for MSI-H or dMMR tumors, or 2) third-line or subsequent therapy as a single agent for PD-L1 positive adenocarcinoma (category 2A). These guidelines recommend that Keytruda be a treatment option in patients with esophageal cancer if PD-L1 expression is ≥ 1; this is in addition to the GEJ adenocarcinomas.[29]

In one Phase II, multicenter, open-label, pivotal study (Keynote-059), Keytruda therapy was evaluated in 259 adults ≥ 18 years of age with gastric or GEJ adenocarcinoma who progressed on two or more prior systemic chemotherapies for advanced disease.[1,30] Patients had previously been treated with a fluoropyrimidine and platinum doublet. Patients with HER2/neu positive disease had received therapy with HER2/neu-targeted therapy. Keytruda 200 mg intravenously was given every 3 weeks. Patients without disease progression were treated for up to 24 months. The major efficacy outcome measures were ORR using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1), assessed by blinded independent central review, and duration of response. In the 259 patients, 55% (n = 143/259) had tumors expressing PD-L1 with a CPS of ≥ 1 and either microsatellite stable (MSS) tumor status or undetermined microsatellite instability (MSI) or mismatch repair (MMR) status.[1] Eighty-five percent of patients had M1 disease and 7% had MO disease.[1] In the 259 patients, 51.7% and 48.3% received Keytruda as third-line therapy and fourth-line therapy, respectively.[30] ***Results.*** In the 259 patients, the ORR was 11.6% (95% CI: 8.0%, 16.1%); six patients had a CR.[30] In the 143 patients with tumors expressing PD-L1 and MSS tumor status or undetermined MSI or MMR status, the ORR was 13.3% (95% CI: 8.2, 20.0); 1.4% of patients had a CR and 11.9% had a PR.[1] In the patients who responded (n = 19/143), the duration of response was 2.8+ to 19.4+ months; 58% of patients (n = 11/19) had responses of ≥ 6 months and 26% of patients (n = 5/10) had responses of ≥ 12 months. In all 259 patients, 3% (n = 7/259) had tumors that were

MSI-H. An ORR was observed in four patients, including one with a CR. The duration of response was 5.3+ to 14.1+ months.

In a multi-cohort, Phase 1b study (Keynote-028), patients (n = 23) with PD-L1 positive *esophageal carcinoma* (squamous cell or adenocarcinoma) received Keytruda 10 mg/kg every 2 weeks for up to 2 years or until confirmed disease progression or intolerable toxicity.[38] Patients had been heavily pre-treated for advanced or metastatic disease. Median follow-up was 7 months. The ORR was 30% (95% CI: 13%, 53%). Median duration of response was 15 months (range, 6 to 26 months).

Dosing in Gastric Cancer, Gastroesophageal Junction (GEJ) Cancer, or Esophageal Cancer in Adults. *Dosing must meet the following*: As a single agent, 200 mg as an intravenous infusion over 30 minutes every 3 weeks.[1, 28-29]

The recommended dose is 200 mg given as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.[1] There are no recommended dose reductions in the prescribing information. Management of AEs may require that Keytruda 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 or stable disease as determined by the prescribing physician.

Duration of Therapy in Gastric Cancer, Gastroesophageal Junction (GEJ) Cancer, or Esophageal Cancer in Adults. Indefinite if the patient has a response or stable disease as determined by the prescribing physician.

Labs/Diagnostics. PD-L1 protein expression in gastric cancer, GEJ cancer, or esophageal cancer is determined by using Combined Positive Score (CPS), which is the number of PD-L1 staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100. The specimen should be considered to have PD-L1 expression if CPS ≥ 1. Determination of PD-L1 expression using an FDA-approved test (PD-L1 IHC 22C3 pharmDx Kit [Dako]) is required before initiating therapy with Keytruda. The CPS must be ≥ 1 as determined by the PD-L1 test. Detection of HER2 or HER2/neu protein overexpression or gene amplification is necessary for selection of patients appropriate for Herceptin therapy. See criteria above.

4. Head and Neck Squamous Cell Carcinoma (HNSCC).

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

A) Keytruda is prescribed by or in consultation with an oncologist; AND

B) The patient has recurrent or metastatic non-nasopharyngeal HNSCC; AND

C) The patient meets ONE of the following conditions (i, ii, or iii):

i. The patient has disease progression on or after trying platinum- (cisplatin, carboplatin) containing chemotherapy;[7] OR

ii. The patient has tried chemotherapy for recurrent or metastatic disease (e.g., Erbitux® [cetuximab intravenous infusion], 5-fluorouracil [5-FU], capecitabine, paclitaxel, docetaxel, methotrexate [MTX]); OR

A platinum-containing chemotherapy regimen or other chemotherapy is contraindicated, according to the prescribing physician. D) Keytruda will be used as a single agent.

Keytruda is indicated for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.[1] This indication is approved under accelerated approval based on tumor response rate and durability of response.

The NCCN guidelines on head and neck cancers (version 1.2018)[7] recommend Keytruda as a single agent for second-line or subsequent therapy for non-nasopharyngeal (squamous cell carcinoma with mixed subtypes) if there is disease progression on or after platinum-containing chemotherapy (category 2A), or for previously treated PD-L1 positive recurrent or metastatic nasopharyngeal cancer (category 2B) for 1) patients with newly diagnosed T4b, any N, M0 disease (Stage IVB), unresectable nodal disease with no metastases, or for patients who are unfit for surgery and performance status 3; 2) patients with metastatic (M1) disease at initial presentation or recurrent/persistent disease with distant metastases, or unresectable locoregional recurrence or second primary in patients with performance status 0 to 2 who have received prior radiation therapy; or 3) for patients with unresectable locoregional recurrence without prior radiation and performance status 3 (category 2A). The choice of systemic therapy is based on patient characteristics such as performance status and goals 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 Keytruda was studied in one Phase Ib, multicenter, nonrandomized, open-label, multi-cohort (two cohorts of patients with HNSCC), pivotal trial (Keynote-012), in 174 adults with recurrent or metastatic HNSCC.[1,8-9] Patients had disease progression on or after platinum-containing chemotherapy administered for recurrent or metastatic HNSCC or following platinum-containing chemotherapy given as part of induction, concurrent, or adjuvant therapy. Intravenous Keytruda 10 mg/kg once every 2 weeks (n = 53) or 200 mg once every 3 weeks (n = 121) was given until unacceptable toxicity or disease progression. Patients without disease progression were treated for up to 24 months. Keytruda could be reinitiated for subsequent disease progression and given for up to 1 additional year. The major efficacy outcome measures were ORR using RECIST v1.1 assessed by BICR, and duration of response. The median number of prior lines of therapy was two. ***Results***. The ORR was 16% (95% CI: 11%, 22%); 5% of patients had a CR. The median follow-up was 8.9 months.

In the 28 patients who responded, the median duration of response had not been reached (range, 2.4+ to 27.7+ months); 23 patients had responses for ≥ 6 months. The ORR and duration of response were similar regardless of the dosage regimen and human papillomavirus (HPV) status.

In one Phase II, multicenter trial (Keynote-055) patients with recurrent or metastatic HNSCC received Keytruda 200 mg once every 3 weeks.[10] Patients had progressive disease after receiving a platinum drug and Erbitux. In the 171 patients who were treated, 75% had received ≥ two prior lines of therapy for metastatic disease, 82% of patients were PD-L1 positive, and 22% were HPV positive. At the time of data analysis, the median follow-up duration was 7 months and 21% of patients (n = 36/171) were still receiving Keytruda. The ORR was 16% (95% CI: 11%, 23%) and the median duration of response was 8 months (range, 2+ to 12+ months). At the time of analysis, 75% of responses were ongoing. Median PFS was 2.1 months and overall survival was 8 months.

Dosing in Recurrent or Metastatic HNSCC in Adults. *Dosing must meet the following*: As a single agent, 200 mg as an intravenous infusion over 30 minutes every 3 weeks.[1]

The recommended dose is 200 mg given as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.[1] There are no recommended dose reductions in the prescribing information. Management of AEs may require that Keytruda 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 or stable disease as determined by the prescribing physician.

Duration of Therapy in Recurrent or Metastatic HNSCC Adults. Indefinite if the patient has a response or stable disease as determined by the prescribing physician.

In the pivotal trial (KEYNOTE-012), which is ongoing, patients without disease progression were treated for up to 24 months.[1] Therapy with Keytruda could be reinitiated for subsequent disease progression and given for up to 1 additional year.

Labs/Diagnostics. None required.

5. Melanoma.

Criteria. *The patient must meet the following criteria (A, B, AND C):*
- **A)** Keytruda is prescribed by or in consultation with an oncologist; AND
- **B)** The patient has unresectable, advanced, or metastatic melanoma; AND
- **C)** Keytruda will not be used in combination with Yervoy® (ipilimumab intravenous infusion).

Keytruda is indicated for the treatment of patients with unresectable or metastatic melanoma.[1]

The NCCN guidelines on melanoma (version 2.2018)[11] recommend Keytruda as single-agent therapy as follows:

- For metastatic or unresectable disease as first-line therapy (category 1);
- For second-line or subsequent therapy after disease progression or maximum clinical benefit from *BRAF* targeted therapy if anti PD-1 therapy not previously used;
- For second-line or subsequent therapy after disease progression or maximum clinical benefit from *BRAF* targeted therapy if prior anti-PD1 therapy resulted in disease control (CR, PR, or stable disease) and no residual toxicity, and disease progression/relapse occurred > 3 months after the treatment was stopped.

Yervoy naïve melanoma. In one Phase III pivotal study (Keynote-006), patients with unresectable or metastatic Stage III or IV melanoma were randomized to receive Keytruda 10 mg/kg every 2 weeks (n = 279) or every 3 weeks (n = 277) until disease progression, unacceptable toxicity or 24 months, or to Yervoy 3 mg/kg once every 3 weeks for 4 cycles (n = 278) unless discontinued earlier for disease progression or unacceptable toxicity.[1,12] Patients with a CR lasting ≥ 6 months could discontinue after an additional two treatments. Patients had received a maximum of one previous systemic therapy for advanced disease. ***Results***. Data are from the first interim analysis **(≥** 260 patients had disease progression or died in all study groups), except for overall survival which is from the second interim analysis (after ≥ 290 patients had died in all study groups). The median duration of follow-up was 7.9 months (range, 6.1 to 11.5 months). Median estimates of PFS were 5.5 months (95% CI: 3.4, 6.9) for Keytruda every 2 weeks, 4.1 months (95% CI: 2.9, 6.9) for Keytruda every 3 weeks, and 2.8 months (95% CI: 2.8, 2.9) for Yervoy.[1] The hazard ratio (HR) for disease progression for both Keytruda regimens vs. Yervoy was 0.58 (P < 0.001).[1] The benefit in PFS for Keytruda over Yervoy was observed in the PD-L1-positive and PD-L1-negative subgroups. At the time of data cutoff for the second interim analysis, 289 deaths had occurred. Estimated 12-month survival rates were 74.1%, 68.4%, and 58.2%, respectively, for patients receiving Keytruda every 2 weeks, Keytruda every 3 weeks, or Yervoy.[12] The HR for death for Keytruda every 2 weeks vs. Yervoy was 0.63 (95% CI: 0.47, 0.83; P < 0.001). The HR for overall survival for Keytruda every 3 weeks vs. Yervoy was 0.69 (95% CI: 0.52, 0.90; P = 0.004).[1,12] In the 94 patients receiving Keytruda 10 mg/kg every 2 weeks with an objective response, response durations ranged from 1.4+ to 8.2 months.[1]

In one Phase II, pivotal, open-label, international trial (Keynote-002), patients with *Yervoy-refractory* melanoma were randomized to receive Keytruda 2 mg/kg (n = 180) or Keytruda 10 mg/kg (n = 181) every 3 weeks, or investigator choice chemotherapy (n = 179).[1,14] Patients had unresectable or metastatic melanoma with progressive disease within 24 weeks after ≥ two Yervoy doses of 3 mg/kg or higher and, if *BRAF V600* mutation-positive, previous treatment with a BRAF or mitogen-activated extracellular signal-regulated kinase (MEK) inhibitor or both. In the chemotherapy group, 48% of patients (n = 86/179) who had progressive disease at or after Week 12, crossed over to Keytruda therapy. ***Results*** are for a prespecified second interim analysis of PFS in the intent-to-treat (ITT) population. Based on 410 PFS events, PFS was improved in patients who received Keytruda 2 mg/kg (HR 0.57; 95% CI: 0.45, 0.73; P < 0.001) and in patients on Keytruda 10 mg/kg (HR 0.50; 95% CI: 0.39, 0.64; P < 0.001) compared with patients on chemotherapy. Six-month PFS was 34% (95% CI: 27%, 41%), 38% (95% CI: 31%, 45%), and 16% (95% CI: 10%, 22%) in the Keytruda 2 mg/kg,

Keytruda 10 mg/kg, and chemotherapy groups, respectively.[14] The ORR was 21% with Keytruda 2 mg/kg every 3 weeks, 25% with Keytruda 10 mg/kg every 3 weeks, and 4% with Yervoy.[1] In the 38 patients on Keytruda 2 mg/kg with an objective response, response duration ranged from 1.3+ to 11.5+ months. In the 46 patients on Keytruda 10 mg/kg with an objective response, response durations ranged from 1.1+ to 11.1+ months. At the time of analysis, the percentage of responders was as follows: 92% (n = 35/38) on Keytruda 2 mg/kg, 87% (n = 40/46) on Keytruda 10 mg/kg, and 63% (n = 5/8) on chemotherapy remained progression free.[14] In an interim analysis of overall survival with 220 deaths (59% of required events for final analysis), there was no statistically significant difference between Keytruda 2 mg/kg and chemotherapy and also no statistically significant difference between Keytruda 10 mg/kg and chemotherapy.[1]

In one Phase III trial, Keytruda 200 mg every 3 weeks (n = 514) was compared with placebo (n = 505) as adjuvant therapy in patients with completely resected, high-risk Stage III melanoma.[44] Keytruda or placebo were given for a total of 18 doses (about 1 year) or until disease recurrence or unacceptable toxicity. After a median follow-up of 15 months, the 1-year rate of recurrence-free survival in the *overall intent-to-treat population* was 75.4% (95% CI: 71.3%, 78.9%) with Keytruda vs. 61.0% (95% CI: 56.5%, 65.1%) with placebo (hazard ratio [HR] for recurrence or death, 0.57; 98.4% CI: 0.43, 0.74; P < 0.001). In the *patients with PD-L1-positive tumors* (n = 853), the 1-year rate of recurrence-free survival was 77.1% (95% CI: 72.7%, 80.7%) with Keytruda vs. 62.6% (95% CI: 57.7%, 67.0%) with placebo (HR, 0.54; 95% CI: 0.42, 0.69; P < 0.001). The most recent NCCN melanoma guidelines do not address adjuvant use of Keytruda.

Dosing in Advanced, Unresectable or Metastatic Melanoma in Adults. *Dosing must meet the following*: As a single agent, 200 mg as an intravenous infusion over 30 minutes every 3 weeks.

The recommended dose is 200 mg given as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity.[1] There are no recommended dose reductions in the prescribing information. Management of AEs may require that Keytruda 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 or stable disease as determined by the prescribing physician.

Duration of Therapy in Advanced, Unresectable or Metastatic Melanoma in Adults. Indefinite if the patient has a response or stable disease as determined by the prescribing physician.

Labs/Diagnostics. None required.

6. Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors.

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

A) Keytruda is prescribed by or in consultation with an oncologist; AND
B) The patient has unresectable or metastatic cancer;[1,15-16] AND
C) Keytruda will be used as single-agent therapy; AND

D) One of the following conditions apply (i or ii):
- **i.** The patient has colorectal cancer (CRC), and one of the following applies a, b, or c);
  - **a)** The patient's CRC has progressed after treatment with a fluoropyrimidine (e.g., 5-fluorouracil [5-FU], capecitabine), oxaliplatin, or irinotecan[15-16] AND the patient has not previously been treated with Keytruda or Opdivo;[1] OR
  - **b)** The patient has had adjuvant therapy with FOLFOX (5-FU, leucovorin, and oxaliplatin) OR CapeOX (capecitabine and oxaliplatin);[15-16] OR
  - **c)** The patient is not a candidate for intensive therapy, according to the prescribing physician.
    OR
- **ii.** For solid tumors other than colorectal cancer (CRC) for example, gastric, gastroesophageal, or esophageal cancers, Ewing sarcoma, mesenchymal chondrosarcoma, pancreatic adenocarcinoma, endometrioid carcinomas,, the following criteria apply (a and b):
  - **a)** The disease has progressed after treatment;[1] AND
  - **b)** There is no satisfactory alternative treatment option, according to the prescribing physician.[1]

AND
E) If the patient is a child, the cancer is not a central nervous system tumor.[1]

Keytruda is indicated for the treatment of adult and pediatric patients with unresectable or metastatic, MSI-H or dMMR solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, OR for CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.[1] Efficacy for pediatric patients with MSI-H or dMMR tumors is extrapolated from the results in the adult population. This indication is approved under accelerated approval based on tumor response rate and durability of response. *Limitation of Use:* The safety and effectiveness of Keytruda in pediatric patients with MSI-H central nervous system cancers have not been established.

The NCCN guidelines on colon cancer (version 2.2018)[15] and rectal cancer (version 1.2018)[16] recommend Keytruda as a single agent for the following: 1) unresectable metachronous metastases (dMMR/MSI-H only) and previous adjuvant FOLFOX (5-FU, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) within the past 12 months, 2) initial therapy for patients with unresectable advanced or metastatic disease (dMMR/MSI-H only) who are not appropriate for intensive therapy, or 3) subsequent therapy (if Opdivo or Keytruda have not been given previously) for unresectable advanced or metastatic disease (dMMR/MSI-H only) after prior oxaliplatin-, irinotecan-, and/or fluoropyrimidine-based therapy (all of these are category 2A recommendations). The NCCN panel recommends universal MMR or MSI testing for all patients with a personal history of colon or rectal cancer to identify patients with Lynch syndrome who may be candidates for immunotherapy and also to inform decisions for patients with Stage II disease. The NCCN panel

recommends Keytruda or Opdivo as treatment options in patients with metastatic dMMR CRC as second or third line therapy. Patients who progress on one of these drugs should not be treated with the other. Keytruda or Opdivo are not recommended as adjuvant therapy in patients with Stage II or III CRC unless they are being used in a clinical trial setting.

The NCCN guidelines address use of Keytruda for many MSI-H or dMMR solid tumors as follows:

- Bone cancer (version 2.2018) recommends single-agent therapy for patients with Ewing sarcoma, mesenchymal chondrosarcoma, osteosarcoma, dedifferentiated chondrosarcoma, or high grade undifferentiated pleomorphic sarcoma that is unresectable or metastatic MSI-H or dMMR that have progressed following prior therapy and have no satisfactory alternative treatment options (category 2A).[31]
- Pancreatic adenocarcinoma (version 1.2018) recommends single-agent therapy for MSI-H or dMMR tumors only for patients with good performance status for one of the following: local recurrence in the pancreatic bed after resection; metastatic disease with or without local recurrence if ≥ 6 months from completion of primary therapy; and metastatic disease with or without local recurrence if < 6 months from completion of primary therapy (all are category 2A).[32]
- Uterine neoplasms (version 2.2018) recommends treatment of patients with recurrent, metastatic or high risk MSI-H or dMMR endometrioid carcinomas that have progressed after cytotoxic chemotherapy (category 2A).[33]
- Cervical cancer (version 1.2018) recommends second-line therapy for treatment of patients with recurrent or metastatic MSI-H or dMMR tumors (category 2B).[46]
- Hepatobiliary cancers (version 2.2018) recommends Keytruda for primary treatment of patients with adenocarcinoma of the gallbladder or cholangiocarcinoma (intrahepatic or extrahepatic), as a single agent for unresectable or metastatic disease that is MSI-H (category 2A).[4]
- Testicular cancer (version 2.2018) recommends single agent palliative therapy in patients with MSI-H/dMMR tumors and progression after prior high-dose chemotherapy or third-line therapy (category 2A).[4]
- Vulvar cancer (version 1.2018) recommends Keytruda for squamous cell carcinoma as second-line therapy for patients with advanced, recurrent or metastatic MSI-H or dMMR tumors (category 2B).[4]
- Ovarian cancer/fallopian tube cancer/primary peritoneal cancer (version 2.2018) recommends Keytruda for epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer as single-agent therapy for persistent disease or recurrence if MSI-H or dMMR. The recommendations are category 2A for clinical relapse and category 2B for immediate treatment of biochemical relapse.[4]
- Penile cancer (version 2.2018) recommends considering for select patients as a single agent as subsequent-line systemic therapy if unresectable or metastatic MSI-H or dMMR tumor that has progressed after prior treatment and no satisfactory alternative treatment options (category 2A).[4]
- Prostate cancer (version 2.2018) recommends subsequent therapy as a single agent for patients who have progressed through at least one line of systemic therapy for castration-resistant distant metastatic (M1) disease that is MSI-H or dMMR, if Keytruda has not been previously received (category 2B).[4]

- Neuroendocrine and adrenal tumors (version 2.2018) recommends considering for the management of dMMR or MSI-H unresectable/metastatic adrenocortical tumors that have progressed following prior treatment and have no satisfactory alternative treatment options (category 2A).[4]

The efficacy of Keytruda was evaluated in patients with MSI-H or dMMR solid tumors enrolled in five uncontrolled, open-label, multi-cohort, multicenter, single-arm pivotal trials.[1] Patients received either Keytruda 200 mg/kg every 3 weeks or Keytruda 10 mg/kg every 2 weeks. Treatment was continued until unacceptable toxicity or disease progression that was either symptomatic, rapidly progressive, required urgent intervention, or occurred with a decrease in performance status. Keytruda was given for a maximum of 24 months. The major efficacy endpoint was ORR assessed by blinded independent central radiologists' review using RECIST 1.1 and duration of response.

Table 1. MSI-H or dMMR Cancer Trials Using Keytruda.[1]

Study	Design and Patient Population	Number of Patients	MSI-H/dMMR Testing	Dose of Keytruda	Prior Therapy
Keynote-016	• Prospective, investigator initiated • Six sites • Patients with CRC and other tumors	N = 28 CRC N = 30 non-CRC	Local PCR or IHC	10 mg/kg every 2 weeks	• CRC: ≥ two prior regimens • Non-CRC: ≥ one prior regimen
Keynote-164	• Prospective international multicenter • CRC	N = 61	Local PRC or IHC	200 mg every 3 weeks	Prior fluoropyrimi-dine, oxaliplatin, and irinotecan +/- anti-VEGF/EGFR mAb
Keynote-012	• Retrospectively identified patients with PD-L1 positive gastric, bladder, or triple-negative breast cancer	N = 6	Central PCR	10 mg/kg every 2 weeks	≥ one prior regimen
Keynote-028	• Retrospectively identified patients with PD-L1 positive esophageal, biliary, breast, endometrial, or CRC	N = 5	Central PCR	10 mg/kg every 2 weeks	≥ one prior regimen
Keynote-0158	• Prospective international multicenter enrollment of patients with MSI-H/dMMR non-CRC • Retrospectively identified patients who were enrolled in specific rare tumor non-CRC cohorts	N = 19	Local PCR or IHC (central PCR for patients in rare tumor non-CRC cohorts)	200 mg every 3 weeks	≥ one prior regimen

MSI-H/dMMR – Microsatellite instability-high/mismatch repair deficient; CRC – Colorectal cancer; PCR – Polymerase chain reaction; IHC – Immunohistology; VEGF/EGFR mAb – Vascular endothelial growth factor/epidermal growth factor receptor monoclonal antibody; PD-L1 – Programmed death-ligand 1.

In all, 149 patients with MSI-H or dMMR cancers were identified in the five clinical trials. In all, 98% of patients had metastatic disease and 2% had locally advanced, unresectable disease. The median number of prior therapies for metastatic or unresectable disease was two. In most of the patients (n = 135/149), the identification of MSI-H or dMMR tumor status was prospectively determined using local laboratory developed polymerase chain reaction (PCR) tests for MSI-H status or immunohistochemistry (IHC) tests for dMMR. Fourteen of the 149 patients were retrospectively identified as MSI-H by testing tumor samples from a total of 415 patients using a central laboratory developed PCR test. Forty-seven patients had dMMR cancer identified by IHC, 60 patients had MSI-

H identified by PCR, and 42 patients were identified using both tests. ***Results***. The ORR was 39.6% (95% CI: 31.7%, 47.9%) with 7.4% of patients having a CR and 32.2% having a PR. In patients with CRC, the ORR was 36% (95% CI: 26%, 46%). In patients with other non-CRC tumors, the ORR was 46% (95% CI: 33%, 59%). The non-CRC tumors (n = 59) included the following cancers: endometrial, biliary, gastric or gastroesophageal junction, pancreatic, small intestinal, bladder, esophageal, sarcoma, thyroid, retroperitoneal adenocarcinoma, small cell lung, and renal cell. The median duration of response was not reached; 78% of patients had a response duration of ≥ 6 months.

Preliminary results were published from Keynote-016.[17] This was a Phase II trial in patients with treatment-refractory progressive metastatic cancer were recruited from three centers. Three cohorts were evaluated: Cohort A included patients (n = 10) with dMMR colorectal adenocarcinomas, Cohort B included patients (n = 18) with mismatch repair-proficient colorectal adenocarcinomas, and Cohort C included patients (n = 7) with dMMR cancers of types other than colorectal. The immune-related ORR were 40% (95% CI: 12%, 74%) in the dMMR CRC group, 0% (95% CI: 0%, 19%) in the MMR-proficient CRC group, 71% (95% CI: 29%, 96%) in the dMMR non-CRC group. Median duration of response was not reached in patients in Cohorts A and C.

Dosing in MSI-H or dMMR Solid Tumors. *Dosing must meet the following (A OR B)*:

- **A)** Adults: As a single agent, 200 mg as an intravenous infusion over 30 minutes every 3 weeks; OR
- **B)** Pediatric patients: As a single agent, 2 mg per kg (up to a maximum of 200 mg) as an intravenous infusion over 30 minutes every 3 weeks.

The recommended dose in adults is 200 mg given as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity or up to 24 months in patients without disease progression.[1] The recommended dose in pediatric patients is 2 mg/kg (up to a maximum of 200 mg) given as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity or up to 24 months in patients without disease progression.[1] There are no recommended dose reductions in the prescribing information. Management of AEs may require that Keytruda 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 or stable disease as determined by the prescribing physician.

Duration of Therapy in MSI-H or dMMR Solid Tumors Solid Tumors. Indefinite if the patient has a response or stable disease as determined by the prescribing physician.

Labs/Diagnostics. Identification of microsatellite instability-High (MSI-H) or mismatch repair deficient (dMMR) tumor status is required before initiating therapy with Keytruda.

7. Non-Small Cell Lung Cancer.

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

- **A)** Keytruda is prescribed by or in consultation with an oncologist; AND
- **B)** The patient has metastatic disease; AND
- **C)** 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 conditions are met (a and b):
    - **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;

      AND
    - **b)** One of the following criteria applies (1, 2, OR 3):
      - **(1)** The patient's tumor proportion score (TPS) for PD-L1 as determined by a FDA-approved test is ≥ 50% AND Keytruda will be used as a single agent; OR
      - **(2)** The patient's tumor proportion score (TPS) for PD-L1 as determined by a FDA-approved test is ≥ 1% AND the patient meets ALL of the following:
        - Systemic chemotherapy has been tried (e.g., cisplatin, carboplatin, Alimta [pemetrexed for intravenous injection], gemcitabine, paclitaxel); AND
        - The patient has not previously been treated with Keytruda, Opdivo (nivolumab), or Tecentriq® (atezolizumab injection for intravenous use); AND
        - Keytruda will be used as a single agent.

        OR
      - **(3)** Keytruda will be used in combination with Alimta (pemetrexed) and carboplatin.

  OR
  - **ii.** Squamous cell carcinoma AND the following conditions are met (a and b):
    - **a)** Keytruda will be used as single-drug therapy; AND
    - **b)** One of the following criteria applies (1 or 2):
      1) The patient's tumor proportion score (TPS) for programmed death-ligand 1 (PD-L1) as determined by a FDA-approved test is ≥ 50%; OR
      2) The patient's tumor proportion score (TPS) for PD-L1 as determined by a FDA-approved test is ≥ 1% AND the patient meets ALL of the following:
         - Systemic chemotherapy has been tried (e.g., cisplatin, carboplatin, Abraxane® [paclitaxel albumin bound intravenous injection], gemcitabine, paclitaxel); AND
         - The patient has not previously been treated with Keytruda.

The NCCN guidelines on NSCLC (version 4.2018)[18] recommendations for Keytruda for adenocarcinoma (with mixed subtypes), squamous cell carcinoma, and large cell carcinoma (i.e., either squamous and non-squamous cell NSCLC) are use as single-agent therapy for recurrent or metastatic disease if PD-L1 expression-positive (≥ 50%) as first-line therapy for tumors that are *EGFR*, *ALK*, *ROS1*, and *BRAF* negative or unknown. This recommendation is category 2B for

locoregional recurrence, excluding mediastinal lymph node recurrence with prior radiation therapy, with no evidence of disseminated disease and is category 1 for all other.

Recommendations for Keytruda for adenocarcinoma (with mixed subtypes), squamous cell carcinoma, and large cell carcinoma are 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 and tumors with PD-L1 expression levels ≥ 1%:

- following progression on initial cytotoxic therapy (category 1); or
- for further progression on other systemic therapy (category 2A).

Recommendations for Keytruda for adenocarcinoma (with mixed subtypes) or large cell carcinoma (i.e., non-squamous cell histology) are as treatment for recurrent or metastatic disease in combination with Alimta and either carboplatin or cisplatin (if Keytruda not previously given) in patients with performance status 0 to 1 as one of the following:

- initial cytotoxic therapy for *EGFR*, *ALK*, *ROS1*, *BRAF* negative or unknown and PD-L1 < 50% **or** unknown; or
- first-line or subsequent therapy for *BRAF V600E*-mutation positive tumors; or
- subsequent therapy for sensitizing *EGFR* mutation-positive tumors and prior Tarceva® (erlotinib tablets), Gilotrif® (afatinib tablets), Iressa® (gefitinib tablets), or Tagrisso® (osimertinib tablets) therapy; or
- subsequent therapy for *ALK* rearrangement-positive tumors and prior Xalkori® (crizotinib capsules), Zykadia™ (ceritinib capsules), Alecensa® (alectinib capsules), Alunbrig™ (brigatinib tablets) therapy; or
- subsequent therapy for *ROS1* rearrangement-positive tumors and prior Xalkori or Zykadia therapy; or
- subsequent therapy for PD-L1 expression-positive (≥ 50%) and *EGFR*, *ALK*, *ROS1* and *BRAF* negative or unknown tumors.

The NCCN guidelines have not been updated to include the results of the Keynote-189 trial[52] (see description below). The approval of Alimta plus Keytruda and carboplatin for first-line therapy for metastatic NSCLC irrespective of PD-L1 expression and no EGFR or ALK was based on the Keynote-021 trial.[53]

In patients with 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.[18] Testing for *ROS1* rearrangements is also recommended (category 2A). Testing for *EGFR* mutations, *ALK* rearrangements, and *ROS1* 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. *EGFR*, *ALK*, and *ROS1* genetic alterations do not usually overlap. *BRAF* mutations typically do not overlap with *EGFR* mutations or *ALK* rearrangements. *BRAF* mutations testing is also recommended. For patients with metastatic NSCLC, the NCCN panel recommends testing for *EGFR* mutations, *BRAF* mutations, *ALK* rearrangements, *ROS1* rearrangements, and PD-L1 expression levels. 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, and *ROS1* rearrangements. The NCCN panel strongly advises broader molecular profiling to identify rare driver mutations to ensure that patients receive appropriate therapy.

In one multicenter, open-label, Phase III trial (Keynote-024), patients with metastatic NSCLC whose tumors had high PD-L1 expression (TPS of ≥ 50%) received Keytruda (n = 154) or a platinum-base chemotherapy regimen (n = 151).[1,19] Patients had not received prior systemic therapy for metastatic NSCLC. Patients with *EGFR* or *ALK* genomic tumor aberrations were excluded. Patients were randomized to Keytruda 200 mg intravenously every 3 weeks or investigator choice of a platinum-containing chemotherapy regimen (Alimta plus carboplatin or cisplatin every 3 weeks for four to six cycles followed by optional Alimta for patients with non-squamous cell NSCLC; gemcitabine plus carboplatin or cisplatin every 3 weeks for 4 to 6 cycles; or paclitaxel plus carboplatin every 3 weeks for four to six cycles followed by optional Alimta maintenance for non-squamous histologies). Keytruda therapy continued until progression of disease determined by an independent radiology committee, unacceptable toxicity, or for up to 24 months. Treatment could continue beyond disease progression if the patient was clinically stable and deriving benefit. Patients randomized to chemotherapy were offered Keytruda when their disease progressed. The primary efficacy endpoint was PFS as assessed by a blinded independent central radiologists' review. In all, 18% of patients had squamous cell histology tumors and 82% had non-squamous cell histology. Also, 66 patients in the chemotherapy arm received Keytruda at the time of disease progression. ***Results***. Median PFS was 10.3 months (95% CI: 6.7, not reached) in the Keytruda arm and 6.0 months (95% CI: 4.2, 6.2) in the chemotherapy arm (HR 0.50; 95% CI: 0.37, 0.68; P < 0.001). A pre-specified interim analysis at 108 events (64% of the events needed for final analysis) showed a statistically significant improvement in overall survival for Keytruda vs. chemotherapy; median overall survival was not reached in the Keytruda arm (95% CI: not reached, not reached) and was not reached in the chemotherapy arm (95% CI: 9.4, not reached) [HR 0.60; 95% CI: 0.41, 0.89; P = 0.005]. The ORR was 45% (95% CI: 37%, 53%) with Keytruda vs. 28% (95% CI: 21%, 36%) with chemotherapy.

In one Phase II/III, multicenter, international study (Keynote-010), patients with previously treated advanced NSCLC with PD-L1 expression on ≥ 1% of tumor cells were randomized 1:1:1 in blocks of six per stratum to Keytruda 2 mg/kg (n = 345), Keytruda 10 mg/kg (n = 345), or docetaxel 75 mg/m^2 (n = 343) every 3 weeks.[1,20] The primary endpoints were overall survival and PFS, both in the total population and in patients with PD-L1 expression on ≥ 50% of tumor cells. Patients were enrolled between August 28, 2013 and February 27, 2015. By September 30, 2015, 521 patients had died. ***Results***. In the total population, median overall survival was 10.4 months, 12.7 months, and 8.5 months with Keytruda 2 mg/kg, Keytruda 10 mg/kg, and docetaxel, respectively. Overall survival was significantly longer for Keytruda 2 mg/kg vs. docetaxel (HR 0.71; 95% CI: 0.58, 0.88; P = 0.0008) and for Keytruda 10 mg/kg vs. docetaxel (HR 0.61; 95% CI: 0.49, 0.75; P < 0.0001). Median PFS survival was 3.9 months with Keytruda 2 mg/kg, 4.0 months with Keytruda 10 mg/kg, and 4.0 months with docetaxel, with no significant difference for Keytruda 2 mg/kg vs. docetaxel (HR 0.88; 95% CI: 0.74, 1.05; P = 0.07) or for Keytruda 10 mg/kg vs. docetaxel (HR 0.79; 95% CI: 0.66, 0.94; P = 0.004). Among patients with ≥ 50% of tumor cells expressing PD-L1, overall survival was significantly longer with Keytruda 2 mg/kg than with docetaxel (median 14.9 vs. 8.2 months; HR 0.54; 95% CI: 0.38, 0.77; P = 0.0002) and with Keytruda 10 mg/kg than with docetaxel (17.3 vs 8.2 months; HR

0.50; 95% CI: 0.36, 0.70; P < 0.0001). Also, for this patient population, PFS was significantly longer with Keytruda 2 mg/kg than with docetaxel (median 5.0 vs. 4.1 months; HR 0.59; 95% CI: 0.44, 0.78; P = 0.0001) and with Keytruda 10 mg/kg than with docetaxel (5.2 vs. 4.1 months; HR 0.59; 95% CI: 0.45, 0.78; P < 0.0001). Grade 3 to 5 treatment-related AEs were less common with Keytruda than with docetaxel (i.e., 13% of patients [n = 43/339] on Keytruda 2 mg/kg, 16% of patients [n = 55/343] on Keytruda 10 mg/kg, and 35% [n = 109/309] on docetaxel).

In another Phase II open-label, multicenter, multi-cohort study (Keynote-021),[1,21] patients with chemotherapy-naïve, Stage IIIB or IV (locally advanced or metastatic) non-squamous cell NSCLC without targetable *EGFR* or *ALK* genetic aberrations were randomized to one of the following regimens: Keytruda 200 mg, carboplatin area under curve (AUC) 5 mg/mL/minute, and Alimta 500 mg/m^2 intravenously (n = 60) every 3 weeks for four cycles followed by Keytruda 200 mg every 3 weeks OR to four cycles of carboplatin AUC 5 mg/mL/minute and Alimta 500 mg/m^2 (n = 63). At the investigators discretion, maintenance Alimta 500 mg/m^2 every 3 weeks could be used in both treatment arms. Assignment was stratified by PD-L1 TPS (< 1% vs ≥ 1%). Positive PD-L1 expression levels were not required for treatment. Treatment with Keytruda continued until RECIST 1.1 defined progression of disease determined by BICR, unacceptable toxicity, or a maximum of 24 months. Patients on chemotherapy could be switched to Keytruda alone at the time of progression. The major efficacy endpoint was ORR assessed by BICR. Other outcome measures were PFS, duration of response, and overall survival. One patient in the Keytruda plus chemotherapy group had Stage IIIB disease.[21] In the chemotherapy group, two patients had Stage IIIB disease and one patient had Stage IIIA disease. PD-L1 TPS was ≥ 50% in 33% of patients on Keytruda plus chemotherapy and in 27% of patients on chemotherapy. PD-L1 TPS was 1% to 49% in 32% of patients on Keytruda plus chemotherapy and in 37% of patients on chemotherapy. PD-L1 TPS was < 1% in 35% of patients in the Keytruda group and in 37% of patients in the chemotherapy group. ***Results*.** At the cutoff date of August 8, 2016, median follow-up was 10.6 months, and 47% of patients (n = 28/59) on Keytruda plus chemotherapy vs. 31% of patients (n = 19/62) were still on their assigned study treatment.[21] Alimta maintenance therapy was received in 85% of patients (n = 50/59) on Keytruda plus chemotherapy and 69% (n = 43/62) on chemotherapy. The ORR was 55% (95% CI: 42%, 68%) in patients receiving Keytruda plus chemotherapy, and 29% (95% CI: 18%, 41%) in patients taking chemotherapy[1,21] (P = 0.0032).[1] There were no CRs.[1,21] PRs were reported in 55% of patients in the Keytruda group and in 29% on chemotherapy with Alimta and carboplatin. Durations of response were ≥ 6 months in 93% of patient on Keytruda combination therapy and 81% of patients on Alimta and carboplatin.[1] Median PFS was 13.0 months (95% CI: 8.3, not estimable) with Keytruda plus chemotherapy and 8.9 months (95% CI: 4.4, 10.3) with chemotherapy (HR 0.53; 95% CI: 0.31, 0.91; P = 0.02).[1,21] In the TPS < 1% subgroup, the ORR was 57% in the Keytruda containing arm and 13.0% in the chemotherapy arm. In the TPS ≥ 1% subgroup, the ORR was 54% in the Keytruda containing arm and 38% in the chemotherapy arm.[1] The authors of the study concluded that in view of the small sample sizes of the individual PD-L1 subgroups, it is not possible to conclusively determine whether there is a relationship between PD-L1 expression and efficacy in patients treated with Keytruda plus chemotherapy. At the time of data cutoff, 22% of patients in each group had died. No difference in survival was noted between the two treatment groups. After 6 months there was a high degree of censoring.

In one Phase III, double-blind trial (Keynote-189), patients (n = 616) with previously untreated metastatic non-squamous NSCLC without sensitizing *EGFR* or *ALK* mutations were randomized to receive Alimta 500 mg/m^2 and a platinum drug (cisplatin or carboplatin) plus either Keytruda 200 mg or placebo every 3 weeks for four cycles.[52] This was followed by Keytruda or placebo for up to total of 35 cycles plus Alimta maintenance therapy given every 3 weeks. Patients in the placebo/ combination group who had disease progression could be crossed over to Keytruda monotherapy. The primary endpoints were overall survival and PFS assessed by BICR. ***Results***. After a median follow-up of 10.5 months, median overall survival was not reached in the Keytruda group and was 11.3 months in the placebo arm. The estimated rate of overall survival at 12 months was 69.2% (95% CI: 64.1%, 73.8%) with Keytruda/combination vs. 49.4% (95% CI: 42.1%, 56.2%) in the placebo/ combination group (HR for death 0.49; 95% CI: 0.38, 0.64; P < 0.001). Improvement in overall survival was reported across all PD-L1 categories. Median PFS was 8.8 months (95% CI: 7.6, 9.2) with Keytruda/combination vs. 4.9 months (95% CI: 4.7, 5.5) with placebo/combination (HR for disease progression or death 0.52; 95% CI: 0.43, 0.64; P < 0.001).

Dosing in NSCLC in Adults. *Dosing must meet the following*: 200 mg as an intravenous infusion over 30 minutes every 3 weeks.

The recommended dose of Keytruda is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. When giving Keytruda in combination with chemotherapy, Keytruda should be given prior to chemotherapy when given on the same day. Management of AEs may require that Keytruda 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 or stable disease as determined by the prescribing physician.

Duration of Therapy in Adults. Indefinite if the patient has a response or stable disease as determined by the prescribing physician.

Labs/Diagnostics.

Determination of PD-L1 expression using an FDA-approved test is required before initiating therapy with Keytruda for two of its indications in NSCLC. PD-L1 expression in NSCLC is determined by using Tumor Proportion Score (TPS), which is the percentage of viable tumor cells showing partial or complete membrane staining at any intensity. The specimen should be considered to have PD-L1 expression if TPS ≥ 1% and high PD-L1 expression if TPS ≥ 50%. For first-line treatment, the TPS must be ≥ 50% tumor cells as determined by the PD-L1 IHC 22C3 pharmDx kit. In patients with disease progression on or after systemic chemotherapy, the TPS must be ≥ 1% as determined by the PD-L1 IHC 22C3 pharmDx kit. Determination of PD-L1 expression is not required for first-line use of Keytruda in combination with Alimta and carboplatin. Detection of *EGFR* mutations and *ALK* fusions is necessary for selection of patients appropriate for targeted therapies prior to using Keytruda therapy. This applies to patients initiating therapy with Keytruda. See criteria above.

8. Primary Mediastinal Large B-Cell Lymphoma (PMBCL).

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

A) Keytruda is prescribed by or in consultation with an oncologist; AND

B) The patient has relapsed after, or is refractory to, at least two lines of therapy (e.g., autologous hematopoietic stem cell transplant [auto-HSCT], EPOCH-R [etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, Rituxan {rituximab injection}], RCHOP [Rituxan, cyclophosphamide, doxorubicin, vincristine, prednisone], RCEPP [Rituxan, cyclophosphamide, doxorubicin, vincristine, prednisone]).

The NCCN clinical practice guidelines on B-cell lymphomas (version 4.2018) recommend Keytruda for diffuse large B-cell lymphoma as treatment for relapsed or refractory PMBCL (category 2A).[39] First-line treatment regimens have included EPOCH-R and RCHOP.

In one multicenter, Phase II trial (Keynote-170), Keytruda was evaluated in adults with PMBCL who had relapsed after auto-HSCT or who were ineligible for auto-HSCT; patients who were ineligible for auto-HSCT had relapsed or refractory disease after ≥ two lines of prior therapy.[1,40] Patients received Keytruda 200 mg intravenously every 3 weeks until disease progression, unacceptable toxicity, or after completing about 2 years. Fifty-three (53) patients were accrued; median age was 33 years (range, 20 to 61 years).[1] Median number of prior lines of therapy was three; 36% of patients had primary refractory disease, 49% had relapsed disease refractory to the last prior therapy, and 15% had untreated relapse. Twenty-six (26%) of patients had had an auto-HSCT. ***Results***. The ORR was 45% (95% CI: 32%, 60%) with 11% of patients having a CR and 34% a PR. With a median follow-up of 9.7 months, median duration of response was not reached (range, 1.1+, 19.2+ months). In a published abstract of this trial, median duration of follow-up was 10.5 months.[40] In 29 patients, the ORR was 41% by BICR (four CRs, eight PRs, and three patients with stable disease). Median duration of response was not reached (range, 1.1 to 8.2 months).

In a multicohort Phase Ib trial (Keynote-013), 17 adult patients with relapsed or refractory PMBCL received Keytruda 20 mg/kg intravenously every 2 weeks or 200 mg every 3 weeks.[41] Patients had failed, were ineligible for, or refused auto-SCT. The ORR was 41% (2 patients with CRs and 5 patients had PRs).

Efficacy of Keytruda for pediatric patients with PMBCL is extrapolated from the results in the adult population.[1]

Dosing in PMBCL. *Dosing must meet ONE of the following (A OR B)*:[1]

A) Adults: As a single agent, 200 mg as an intravenous infusion over 30 minutes every 3 weeks; OR

B) Pediatric Patients: As a single agent, 2 mg per kg (up to a maximum of 200 mg) as an intravenous infusion over 30 minutes every 3 weeks.

The recommended dose in adults is 200 mg given as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity or up to 24 months in patients without disease progression.[1] The recommended dose in pediatric patients is 2 mg/kg (up to a maximum of

200 mg) given as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity or up to 24 months in patients without disease progression.[1] There are no recommended dose reductions in the prescribing information. Management of AEs may require that Keytruda 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 PMBCL. Indefinite if the patient has a response or stable disease as determined by the prescribing physician.

Labs/Diagnostics. None required.

9. Urothelial Carcinoma.

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

A) Keytruda is prescribed by or in consultation with an oncologist; AND

B) The patient has locally advanced or metastatic urothelial carcinoma; AND

C) Keytruda will be used as a single agent; AND

D) The patient meets ONE of the following conditions (i or ii):

- **i.** The patient is not eligible for cisplatin-based chemotherapy, according to the prescribing physician; OR
- **ii.** The patient has disease progression during or after trying platinum- (cisplatin, carboplatin) containing chemotherapy.

Keytruda is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy.[1] This indication is approved under accelerated approval based on tumor response rate and durability of response. Keytruda is also indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

The NCCN guidelines on bladder cancer (version 4.2018) recommend Keytruda for urothelial carcinoma of the *bladder* as first-line systemic therapy as a single agent in cisplatin ineligible patients for locally advanced or metastatic disease (Stage IV) [preferred, category 2A]. Keytruda is also recommended for urothelial *bladder* cancer for locally advanced or metastatic disease as subsequent systemic therapy post-platinum (preferred) [category 1].[3,22] Keytruda is also recommended as a single agent for urothelial carcinoma as first-line therapy in cisplatin ineligible patients or as subsequent systemic therapy post platinum therapy 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 of the standard neoadjuvant or

adjuvant regimens recommended for systemic therapy include cisplatin (i.e., DDMVAC [dose-dense MTX, vinblastine, doxorubicin, and cisplatin] with growth factor support, gemcitabine plus cisplatin, CMV [cisplatin, MTX, and vinblastine]). For patients who are not candidates for cisplatin, there are no data supporting a recommendation for neoadjuvant or adjuvant therapy. *First-line systemic chemotherapy* for locally advanced or metastatic disease *in patients who are eligible for cisplatin*, include gemcitabine plus cisplatin (category 1) or DDMVAC with growth factor support (category 1). In patients who are ineligible for cisplatin the preferred regimens are gemcitabine and carboplatin, Tecentriq, or Keytruda. A substantial number of patients cannot receive cisplatin-based chemotherapy due to renal impairment or other comorbidities, and participation in clinical trials of new or more tolerable therapy is recommended. For *subsequent systemic therapy* of locally advanced or metastatic disease participation in clinical trials of new agents is recommended. Keytruda is the preferred regimen (category 1). Tecentriq, Opdivo, Imfinzi™ (durvalumab intravenous injection), and Bavencio® (avelumab intravenous injection) are alternative preferred regimens (category 2A). Alternate regimens for select patients are also listed in the guidelines.

Previously treated urothelial carcinoma. In one open-label, multicenter Phase III trial (Keynote-045), patients with locally advanced or metastatic urothelial carcinoma with disease progression on or after platinum-based chemotherapy were randomized to receive Keytruda 200 mg every 3 weeks (n = 270) or investigator's choice of chemotherapy (paclitaxel, docetaxel, or vinflunine) given every 3 weeks (n = 272).[1,23] Treatment was continued until unacceptable toxicity or disease progression. Patients without disease progression could be treated for up to 24 months. Median follow-up time was 9.0 months. ***Results***. Median overall survival was 10.3 months (95% CI: 8.0, 11.8) with Keytruda vs. 7.4 months (95% CI: 6.1, 8.3) with chemotherapy (HR 0.73; 95% CI: 0.59, 0.91; P = 0.004). PFS was not significantly different between Keytruda and chemotherapy. ORR was 21% (n = 57/270) with Keytruda vs. 11% (n = 30/272) with chemotherapy. Median duration of response was not reached with Keytruda. There was a lower rate of treatment-related AEs with Keytruda than with chemotherapy.

Cisplatin ineligible patients with urothelial carcinoma. In one Phase II open-label multicenter trial (Keynote-052) 370 patients with locally advanced or metastatic urothelial carcinoma who were *not eligible for cisplatin-containing chemotherapy* received 200 mg of Keytruda every 3 weeks until unacceptable toxicity or disease progression.[1] Patients without disease progression could be treated for up to 24 months. The major efficacy outcome measures were ORR assessed by independent radiology review and duration of response. Some of the reasons for ineligibility for cisplatin included 50% of patients with baseline creatinine clearance < 60 mL/minute and 32% of patients with ECOG PS of 2. Ninety percent of patients were treatment naïve and 10% had received prior adjuvant or neoadjuvant platinum-based chemotherapy. On further analysis, 30% of the patients (n = 110/370) had tumors that expressed PD-L1 with a CPS of ≥ 10. Some of the reasons for cisplatin ineligibility in these 110 patients included 45% of patients with baseline creatinine clearance < 60 mL/minute and 37% with ECOG PS of 2. Median follow-up was 7.8 months. ***Results***. In the 370 patients, the ORR was 29% (95% CI: 24%, 34%) with 7% of patients (n = 26/370) having a CR and 22% of patients (n = 81/370) having a PR. In the 110 patients with a CPS of ≥ 10, the ORR was 47% (95% CI: 38%, 57%) with 15% of patients having a CR and 32% have a PR. Median duration of response was not reached in both populations.

Previously untreated urothelial carcinoma. In another ongoing Phase III, multicenter trial (Keynote-361), patients with previously untreated metastatic urothelial carcinoma who are eligible for platinum-containing chemotherapy were randomized to receive Keytruda with or without platinum-based chemotherapy (cisplatin or carboplatin with gemcitabine) or to platinum-based chemotherapy alone.[1] In a third arm to this study, monotherapy with Keytruda was compared with platinum-based chemotherapy alone. An independent Data Monitoring Committee (iDMC) for this trial reviewed early data and found that in patients with low PD-L1 expression (CPS < 10), those receiving Keytruda alone had decreased survival compared with patients receiving platinum-based chemotherapy. The iDMC recommended stopping further accrual of patients with low PD-L1 in the monotherapy arm. No other changes were recommended, including any change of therapy for patients already randomized to and were receiving therapy in the monotherapy arm.

Dosing in Urothelial Carcinoma in Adults. *Dosing must meet the following*: As a single agent, 200 mg as an intravenous infusion over 30 minutes every 3 weeks.

The recommended dose of Keytruda is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. Management of AEs may require that Keytruda 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 or stable disease as determined by the prescribing physician.

Duration of Therapy in Adults. Indefinite if the patienthas a response or stable disease as determined by the prescribing physician.

Labs/Diagnostics. None required

Other Uses with Supportive Evidence

10. Anal Carcinoma.

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

A) Keytruda is prescribed by or in consultation with an oncologist; AND

B) The patient has metastatic squamous cell anal carcinoma;[42] 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) Keytruda will be used as a single agent.

The NCCN guidelines on anal carcinoma (version 2.2018) recommend Keytruda for squamous cell anal carcinoma as second-line or subsequent therapy as a single agent for metastatic disease

(category 2A).[42] Primary treatment for metastatic disease includes 5-FU/cisplatin ± radiation therapy (RT), carboplatin/paclitaxel ± RT, or FOLFOX ± RT.

In one multicohort, phase Ib trial (Keynote-028), patients with PD-L1 positive (≥1%) advanced anal carcinoma received Keytruda 10 mg/kg once every 2 weeks for up to 2 years or until confirmed progression or unacceptable toxicity.[43] ***Results***. Of the 43 patients with advanced anal carcinoma evaluable for PD-L1 expression, 32 (74%) had PD-L1-positive tumors. In the 24 patients with squamous cell carcinoma histology, four patients had confirmed PRs, for an ORR of 17% (95% CI: 5%, 37%) and 10 (42%) had confirmed stable disease, for a disease control rate of 58%. One additional patient with non-squamous histology had confirmed stable disease.

Dosing in Anal Carcinoma in Adults. *Dosing must meet ONE of the following (A OR B)*:
A) As a single agent, 200 mg as an intravenous infusion once every 3 weeks; OR
B) As a single agent, 2 mg per kg as an intravenous infusion once every 3 weeks.

The NCCN guidelines on anal carcinoma recommend a dose of Keytruda 200 mg every 3 weeks or 2 mg/kg every 3 weeks.[42]

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 has a response or stable disease as determined by the prescribing physician.

Labs/Diagnostics. None required.

11. Brain Metastases Due to Melanoma or Non-Small Cell Lung Cancer (NSCLC).

Criteria. *The patient must meet the following criteria (A, B, AND C):*
E) Keytruda is prescribed by or in consultation with an oncologist; AND
F) The patient has recurrent disease and Keytruda is active against the primary melanoma or non-small cell lung cancer (NSCLC) tumor; AND
G) Keytruda will be used as a single agent.

The NCCN guidelines on central nervous system cancers (version 1.2018) recommend single agent Keytruda be used as treatment for *limited brain metastases* in patients with melanoma or NSCLC 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).[34] Keytruda is also recommended as a single agent for treatment of *extensive brain metastases* for recurrent disease in patients with melanoma or NSCLC and stable systemic disease or reasonable systemic treatment options (category 2A).

In one non-randomised, open-label, Phase II trial, patients aged 18 years or older with untreated brain metastases with melanoma or NSCLC received Keytruda 10 mg/kg every 2 weeks until progression.[35] Patients with NSCLC had tumor tissue positive for PD-L1 expression; this was not required for patients with melanoma. The primary endpoint was brain metastasis response assessed in all treated patients. The trial is ongoing. Thirty-six patients with untreated or progressive brain metastases (18 patients with melanoma, 18 with NSCLC) were treated. A brain metastasis response was attained in 22% of patients (n = 4/18) [95% CI: 7%, 48%] with melanoma and 33% of patients (n = 6/18) [95% CI: 14%, 59%] with NSCLC. Responses were durable.

Dosing in Brain Metastases Due to Melanoma or NSCLC in Adults. *Dosing must meet ONE of the following (A OR B)*:

A) As a single agent, 2 mg per kg as an intravenous infusion over 30 minutes every 3 weeks; OR

B) Other dosing will be considered per oncology specialty center protocol.

Keytruda 10 mg/kg every 2 weeks[35-36] and 2 mg/kg every 3 weeks have been used for brain metastases.[36-37]

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 or stable disease, as determined by the prescribing physician.

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

Labs/Diagnostics. None required.

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12. Malignant Pleural Mesothelioma.

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

A) Keytruda is prescribed by or in consultation with an oncologist; AND

B) The patient has tried first-line chemotherapy (e.g., Alimta [pemetrexed intravenous injection] with or without cisplatin or carboplatin, gemcitabine plus cisplatin, vinorelbine); AND

C) Keytruda will be used as a single agent.

The NCCN clinical practice guidelines on malignant pleural mesothelioma (version 2.2018) recommend Keytruda for subsequent systemic therapy as a single agent (category 2A).[26]

In one Phase 1b multicenter, open label study (Keynote-028), patients with PD-L1 positive malignant pleural mesothelioma received Keytruda 10 mg/kg every 2 weeks for up to 2 years or until confirmed progression or unacceptable toxicity.[27] Patients had either failed standard therapy or were unable to receive standard therapy. Patients had PD-L1 expression ≥ 1% in tumor cells and ECOG PS of 0 or 1. As of June 20, 2016, 25 patients had received Keytruda. The confirmed ORR was 20% (95% CI: 6.8%, 40.7%); five patients had a PR and 13 patients had stable disease. Median

duration of response was 12.0 months. Five patients reported Grade 3 treatment related AEs. No treatment related deaths or discontinuations occurred.

Dosing in Malignant Pleural Mesothelioma in Adults. *Dosing must meet the following*: As a single agent, 10 mg per kg as an intravenous infusion every 2 weeks.[27]

In one trial (KEYNOTE-028), Keytruda 10 mg/kg was given every 2 weeks for up to 2 years.[27] Ongoing studies in patients with malignant pleural mesothelioma are using 200 mg of Keytruda every 3 weeks.

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 or stable disease as determined by the prescribing physician.

Duration of Therapy in Adults. Indefinite if the patient has a response or stable disease as determined by the prescribing physician.

Labs/Diagnostics. None required

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13. Melanoma, Uveal.

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

A) Keytruda is prescribed by or in consultation with an oncologist; AND
B) The patient has metastatic or unresectable uveal melanoma.[45]
C) Keytruda will be used as a single agent.[45]

The NCCN guidelines on uveal melanoma (version 1.2018) recommend Keytruda be considered as a single agent therapy for metastatic or unresectable disease (category 2A).[45] 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 Opdivo, Yervoy, dacarbazine, temozolomide, paclitaxel, Abraxane, carboplatin plus paclitaxel, and Mekinist® (trametinib tablets).

In an expanded access program, 25 patients with metastatic uveal melanoma received Keytruda 2 mg/kg intravenously every 3 weeks.[48] All of the patients had received Yervoy. Two patients had a PR and 6 patients had stable disease. With a median follow-up of 225 days, median PFS was 91 days.

In another report, 10 patients with unresectable metastatic uveal melanoma received Keytruda 2 mg/kg every 3 weeks until disease progression, unacceptable toxicity, or for up to 2 years.[49] Patients had progressed on prior Yervoy therapy. As of the data cutoff date, median PFS was 18 weeks (range, 3.14 to 49.3 weeks); four patients were still currently receiving therapy. Of eight

evaluable patients, there was one CR, two PRs, and one patient with stable disease. Four patients had rapidly progressive disease.

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.[50] 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.[51] 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 OR B)*:
A) As a single agent, 2 mg per kg as an intravenous infusion once every 3 weeks;[48-49,51] OR
B) Other dosing regimens will be reviewed on a case-by-case basis.

Keytruda 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, but do not include dosing recommendations. Management of AEs may require that Keytruda 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 has a response or stable disease as determined by the prescribing physician.

Labs/Diagnostics. None required.

14. Merkel Cell Carcinoma.

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

A) Keytruda is prescribed by or in consultation with an oncologist; AND

B) The patient has disseminated disease.[24]

The NCCN clinical practice guidelines on Merkel cell carcinoma (version 2.2018) recommend Keytruda for treatment of disseminated, clinical M1 disease with or without surgery and**/**or radiation therapy (category 2A).[24] For systemic therapy of disseminated disease the guidelines recommend enrollment in a clinical trial (preferred).

In one multicenter, Phase II, uncontrolled study, adults with distant metastatic or recurrent locoregional Merkel cell carcinoma that was not amenable to definitive surgery or radiation therapy and who had not received prior systemic therapy, were given Keytruda 2 mg/kg every 3 weeks intravenously for a maximum of 2 years or until a CR, dose-limiting toxicity, or progressive disease occurred.[25] The primary endpoint was the ORR according to RECIST v1.1. In all, 26 patients received at least one dose of Keytruda. ***Results***. The ORR in the 25 patients with at least one evaluation during treatment was 56% (95% CI: 35%, 76%); four patients had a CR and 10 had a PR. With a median follow-up of 33 weeks (range, 7 to 53 weeks), relapses occurred in 14% of the patients (n = 2/14) who had a response. The duration of response ranged from ≥ 2.2 months to ≥ 9.7 months. PFS at 6 months was 67% (95% CI: 49%, 86%). Responses were reported in patients with virus-positive (i.e., Merkel cell polyomavirus) tumors as well as in virus-negative tumors. Drug-related Grade 3 or 4 AEs occurred in 15% of the patients.

Dosing in Merkel Cell Carcinoma. *Dosing must meet the following*: As a single agent, 2 mg/kg as an intravenous infusion over 30 minutes every 3 weeks.

In one Phase II study, patients received Keytruda 2 mg/kg every 3 weeks.[25]

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 or stable disease, as determined by the prescribing physician.

Duration of Therapy in Merkel Cell Carcinoma. Indefinite if the patient has a response or stable disease as determined by the prescribing physician.

Labs/Diagnostics. None required.

Waste Management for All Indications.

Dosing for Keytruda in pediatric patients with cHL, PMBCL, or MSI-H/dMMR solid tumors is based on body weight (mg/kg). The dose should be calculated and the number of vials needed assessed. Dosing for Keytruda in melanoma, HNSCC, NSCLC, cHL (adults), PMBCL (adults), urothelial carcinoma, MSI-H/dMMR solid tumors (adults), gastric or GEJ cancers, or cervical cancer is 200 mg. The number of vials needed should be calculated and the entire vials are used.

Conditions Not Recommended for Approval
Keytruda 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.

SPECIAL CONSIDERATIONS
None.

LIMITATIONS/EXCLUSIONS
Please refer to a product line's certificate of coverage for benefit limitations and exclusions for these services:

PRODUCT LINE	LINK TO CERTIFICATE OF COVERAGE
MEDICARE ADVANTAGE	http://healthfirst.chpw.org/for-members/resource-library/handbooks-and-guides
WASHINGTON APPLE HEALTH	http://chpw.org/our-plans/apple-health/
INTEGRATED MANAGED CARE	http://chpw.org/our-plans/apple-health/

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CFR	
WAC	WAC 284-43-2050
RCW	
Contract Citation	☐ WAH ☐ IMC ☐ 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
07/24/2017	Criteria completely updated and revised	Michael Sporck, Pharmacy Intern Sophia Yun, PharmD
07/25/2017	Approved	MMLT
03/09/2018	Reassigned from UM to PM	Cindy Bush
04/25/2018	Transferred to new template	Cindy Bush
05/16/18	Revised	Jennifer Farley, PharmD
06/14/2018	Approval	UM Committee
08/03/2018	Revised	Jennifer Farley, PharmD
09/19/2018	Approval	UM Committee