Effective November 1, 2018, refer to Palmetto Article A56141

BlueCross BlueShield of Alabama

"Unless otherwise noted, coverage for specific indications is effective the date of the FDA approval of that indication."
"Please check Approved by Governing Bodies for FDA approval date."

Name of Blue Advantage Policy:
Opdivo® (nivolumab)

Policy #: 660
Category: Pharmacology
Effective Date: March 19, 2018
Latest Review Date: January 2018

Background:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the patient's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the patient's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

Description of Procedure or Service:

Opdivo® (nivolumab) is a programmed death receptor -1 (PD-1) blocking antibody that binds to the PD-1 receptor found on T cells and blocks its interaction with PD-L1 and PD-L2. In some tumors, upregulation of PD-1 ligands can occur, which contributes to the inhibition of active T-cell surveillance of tumors. Nivolumab releases the inhibition of this pathway and allows for the anti-tumor immune response to occur.

Policy:

Effective for dates of service on or after November 1, 2018 refer to Palmetto Article A56141

Effective for dates of service on or after March 19, 2018 and prior to November 1, 2018:

Blue Advantage will treat **Opdivo® (nivolumab)** as a **covered benefit** as **a single agent** for the treatment of **classical Hodgkin lymphoma** when used as additional therapy for relapsed or refractory disease that has been previously treated with brentuximab vedotin or disease that has relapsed or progressed following HDT/ASCR (high-dose therapy and autologous stem cell rescue) and post-transplant brentuximab vedotin.

Blue Advantage will treat **Opdivo® (nivolumab)** as a **covered benefit** when **ALL** of the following are met:

- Has not received treatment with another PD-1 agent (e.g., pembrolizumab); **AND**
- Current Eastern Cooperative Oncology Group (ECOG) performance status of 0-2; **AND**
- Individual does not have an active autoimmune disease or chronic condition requiring systemic immunosuppression; **AND**
- **Follows individual criteria for specific oncologic indication as listed BELOW:**

Colorectal Cancer

Blue Advantage will treat **Opdivo® (nivolumab)** as a **covered benefit** when used as **a single agent** for the treatment of **colorectal cancer** for **any** of the following indications:

- Primary treatment for unresectable metachronous metastases (defective mismatch repair/high microsatellite instability [dMMR/MSI-H] only) and previous adjuvant FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) within the past 12 months; **OR**
- Subsequent therapy (if nivolumab or pembrolizumab not previously given) for unresectable advanced or metastatic disease (defective mismatch repair/high microsatellite instability [dMMR/MSIH] only) following previous treatment with oxaliplatin-irinotecan.

Hepatocellular Carcinoma

Blue Advantage will treat **Opdivo® (nivolumab)** as a **covered benefit** when used as a **single agent** for the treatment of **hepatocellular carcinoma** for disease progression on or have intolerance to sorafenib.

Malignant Pleural Mesothelioma
Blue Advantage will treat **Opdivo® (nivolumab)** as a **covered benefit** for the treatment of m**alignant pleural mesothelioma** for **any** of the following indications:

- when used as a single agent in subsequent therapy or in combination with Yervoy® (ipilimumab); **or**
- Individual is ineligible for platinum-based chemotherapy, defined as having one or more of the following risk factors for platinum-based chemotherapy toxicity:
    - ECOG performance status equal to 2;
    - Glomerular filtration rate less than 60 mL/min;
    - Hearing loss (measured at audiometry) of 25 dB at two contiguous frequencies;
    - Grade 2 or greater peripheral neuropathy

Melanoma
Blue Advantage will treat **Opdivo® (nivolumab)** as a **covered benefit** for the treatment of **unresectable or metastatic melanoma**, excluding primary ocular melanoma, for any of the following indications:

- when used as a single agent, or in combination with ipilimumab, as first-line therapy for untreated melanoma; **or**
- when used as a single agent, or in combination with ipilimumab as second-line or subsequent therapy for documented disease progression while receiving or since completing most recent therapy, if PD-1 agent not previously used; **or**
- when used as adjuvant treatment for up to 12 months for Stage IIIB/C or Stage IV melanoma with lymph node involvement or metastatic disease after complete resection.

Merkel Cell Carcinoma
Blue Advantage will treat **Opdivo® (nivolumab)** as a **covered benefit** when used as a **single agent** for the treatment of **metastatic or recurrent locoregional Merkel cell carcinoma** determined to be not amenable to definitive surgery or radiation therapy.

Non-Small Cell Lung Cancer (NSCLC)
Blue Advantage will treat **Opdivo® (nivolumab)** as a **covered benefit** for the treatment of **metastatic non-small cell lung cancer** when used as a **single agent** (if not already given) for **any** of the following indications:

- For disease progression on or after platinum-containing chemotherapy; **OR**
- For further disease progression on other systemic therapy

Renal Cell Carcinoma
Blue Advantage will treat **Opdivo® (nivolumab)** as a **covered benefit** for the treatment of **advanced renal cell carcinoma** when used as a **single agen**t for **relapsed or surgically unresectable stage IV disease** that has progressed on prior anti-angiogenic therapy for any of the following indications:

- when used as subsequent therapy for predominant clear cell histology; **or**
- when used a systemic therapy for non-clear cell histology

Small Cell Lung Cancer
Blue Advantage will treat **Opdivo® (nivolumab)** as a **covered benefit** for the treatment of **small cell lung cancer** when used as a **single agent** or **in combination with Yervoy (ipilimumab)** for subsequent systemic therapy for **any** of the following indications:

- Relapse within 6 months following complete or partial response or stable disease with initial treatment; **OR**
- Primary progressive disease

Squamous Cell Carcinoma of the Head and Neck (SCCHN)
Blue Advantage will treat **Opdivo® (nivolumab)** as a **covered benefit** for the treatment of **recurrent, unresectable or metastatic squamous cell carcinoma of the head and neck** when being used as a **single agent fo**r disease progression on or after platinum-containing chemotherapy.

Urothelial Carcinoma
Blue Advantage will treat **Opdivo® (nivolumab)** as a **covered benefit** when used as **a single agent** for the treatment of **locally advanced or metastatic urothelial carcinoma** for **any** of the following indications:

- For disease progression on or after platinum-containing chemotherapy; **or**
- For disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

Blue Advantage will treat **Opdivo (nivolumab)** as a **non-covered benefit** and as **investigational** when used in combination with another PD-1 agent (for example, Keytruda [pembrolizumab]).

Blue Advantage will treat **Opdivo (nivolumab)** as a **non-covered benefit** and as **investigational** when the above criteria are not met.

Effective for dates of service April 10, 2017 through March 18, 2018
Blue Advantage will treat **Opdivo® (nivolumab)** as a **covered benefit** for the treatment of **locally advanced or metastatic urothelial carcinoma** for **any** of the following indications:

- For disease progression on or after platinum-containing chemotherapy; **or**
- For disease progression within 12 months of neoadjuvant treatment with platinum-containing chemotherapy.

Blue Advantage will treat **Opdivo® (nivolumab)** as a **covered benefit** for the treatment of **unresectable or metastatic melanoma**, excluding primary ocular melanoma when being used as a **single agent** and the individual does not have an active autoimmune disease and for **any** of the following indications:

- Will be used as a single agent, or in combination with ipilimumab, as first-line therapy for untreated melanoma; **or**

- Will be used as a single agent, or in combination with ipilimumab as second-line or subsequent therapy for documented disease progression while receiving or since completing most recent therapy, if PD-1 agent not previously used; **and**
- Current ECOG performance status of 0-2.

Blue Advantage will treat **Opdivo® (nivolumab)** as a **covered benefit** for the treatment of **metastatic non-small cell lung cancer** when used as a **single agent** (if not already given) in individuals with performance status of 0-2 and do not have an active autoimmune disease for **any** of the following:

- For disease progression on or after platinum-containing chemotherapy; **OR**
- For disease progression on other systemic therapy

Blue Advantage will treat **Opdivo® (nivolumab)** as a **covered benefit** for the treatment of **advanced renal cell carcinoma** when used for subsequent therapy as a **single agen**t for **relapsed or surgically unresectable stage IV disease** that has progressed on prior anti-angiogenic therapy and the individual does not have an active autoimmune disease.

Blue Advantage will treat **Opdivo® (nivolumab)** as a **covered benefit** for the treatment of **classical Hodgkin lymphoma** for **any** of the following:

- Will be used as additional therapy as a **single agent** for refractory or relapsed disease; **OR**
- Will be used for additional therapy as a **single agent** for disease that has relapsed or progressed after an autologous hematopoietic stem cell transplantation (HSCT), high-dose therapy (HDT), and post-transplantation brentuximab vedotin.

Blue Advantage will treat **Opdivo® (nivolumab)** as a **covered benefit** for the treatment of **small cell lung cancer** when used as a **single agent** or **in combination with Yervoy (ipilimumab)** for subsequent systemic therapy in individuals with performance status of 0-2 for **any** of the following:

- Relapse within 6 months following complete or partial response or stable disease with initial treatment; **OR**
- Primary progressive disease

Blue Advantage will treat **Opdivo (nivolumab)** as a **covered benefit for the treatment of recurrent, unresectable, or metastatic squamous cell carcinoma of the head and neck (SCCHN)** when being used as a **single agent**; the individual does not have an active autoimmune disease and all of the following indications:

- For disease progression on or after platinum-containing chemotherapy; **and**
- Current ECOG performance status of 0-2

Blue Advantage will treat **Opdivo (nivolumab)** as a **non-covered benefit** and as **investigational** when used in combination with another PD-1 agent (for example, Keytruda [pembrolizumab]).

Blue Advantage will treat **Opdivo (nivolumab)** as a **non-covered benefit** and as **investigational** when the above criteria are not met.

Effective for dates of service on or after November 8, 2016 and prior to April 10, 2017:
Blue Advantage will treat **Opdivo® (nivolumab)** as a **covered benefit** for the treatment of **unresectable or metastatic melanoma**, excluding primary ocular melanoma when being used as a **single agent** and the individual does not have an active autoimmune disease.

Blue Advantage will treat **Opdivo® (nivolumab)** as a **covered benefit** for the treatment of **unresectable or metastatic melanoma** when used in combination with Yervoy (ipilimumab) for **any** of the following:

- As first-line therapy; **OR**
- As a second line or subsequent therapy for disease progression for patients with performance status 0-2 if not previously used

Blue Advantage will treat **Opdivo® (nivolumab)** as a **covered benefit** for the treatment of **metastatic non-small cell lung cancer** when used as a **single agent** (if not already given) in individuals with performance status of 0-2 and do not have an active autoimmune disease for **any** of the following:

- For disease progression on or after platinum-containing chemotherapy; **OR**
- For disease progression on other systemic therapy

Blue Advantage will treat **Opdivo® (nivolumab)** as a **covered benefit** for the treatment of **advanced renal cell carcinoma** when used for subsequent therapy as a **single agen**t for **relapsed or surgically unresectable stage IV disease** that has progressed on prior anti-angiogenic therapy and the individual does not have an active autoimmune disease.

Blue Advantage will treat **Opdivo® (nivolumab)** as a **covered benefit** for the treatment of **classical Hodgkin lymphoma** for **any** of the following:

- Will be used as additional therapy as a **single agent** for refractory or relapsed disease; **OR**
- Will be used for additional therapy as a **single agent** for disease that has relapsed or progressed after an autologous hematopoietic stem cell transplantation (HSCT), high-dose therapy (HDT), and post-transplantation brentuximab vedotin.

Blue Advantage will treat **Opdivo® (nivolumab)** as a **covered benefit** for the treatment of **small cell lung cancer** when used as a **single agent** or **in combination with Yervoy (ipilimumab)** for subsequent systemic therapy in individuals with performance status of 0-2 for **any** of the following:

- Relapse within 6 months following complete or partial response or stable disease with initial treatment; **OR**
- Primary progressive disease

Blue Advantage will treat **Opdivo (nivolumab)** as a **covered benefit for the treatment of recurrent, unresectable, or metastatic squamous cell carcinoma of the head and neck (SCCHN)** when being used as a **single agent**; the individual does not have an active autoimmune disease and all of the following indications:

- For disease progression on or after platinum-containing chemotherapy; **and**
- Current ECOG performance status of 0-2

Blue Advantage will treat **Opdivo (nivolumab)** as a **non-covered benefit** and as **investigational** when used in combination with another PD-1 agent (for example, Keytruda [pembrolizumab]).

Blue Advantage will treat **Opdivo (nivolumab)** as a **non-covered benefit** and as **investigational** when the above criteria are not met.

Effective for dates of service September 1, 2015 through November 7, 2016:
Blue Advantage will treat **Opdivo® (nivolumab)** as a **covered benefit** for the treatment of **unresectable or metastatic melanoma**, excluding primary ocular melanoma when being used as a **single agent** and the individual does not have an active autoimmune disease.

Blue Advantage will treat **Opdivo® (nivolumab)** as a **covered benefit** for the treatment of **squamous non-small cell lung cancer** with disease progression on or after platinum-containing chemotherapy when used as a single agent and the individual does not have an active autoimmune disease.

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

Metastatic Melanoma (MM)
Melanoma, the most aggressive type of skin cancer, is the leading cause of death from skin cancer. The median survival for individuals with stage IV melanoma is 6-10 months, and less than 5% of individuals survive beyond 5 years. Melanoma is more likely to spread to other parts of the body than other forms of skin cancer and has been on the rise over the past several decades, according to the National Cancer Institute, with an estimated 87,110 new cases and 9,730 deaths from the disease in 2017. In stage III melanoma, the cancer has reached one or more lymph nodes. Patients with stage III melanoma are generally treated by surgery to remove the melanoma skin lesions and the nearby lymph nodes.

The National Comprehensive Cancer Network® (NCCN®) Clinical Practice Guidelines in Oncology on Melanoma (2017) address the challenges with treatment for stage IV melanoma:

> The therapeutic landscape for metastatic melanoma is rapidly changing with the recent development of novel agents, which has demonstrated better efficacy than traditional chemotherapy. The first generation of novel targeted and immunotherapy agents (i.e., vemurafenib, dabrafenib, ipilimumab) demonstrated significantly improved response rates and outcomes compared with conventional therapies. Subsequently, a number of ongoing or recently completed phase II and phase III trials testing new immunotherapies, targeted therapies, and combination regimens have yielded noteworthy results. A second generation of effective agents and combination regimens are now available for treatment of advanced unresectable or metastatic melanoma.

On December 22, 2014, nivolumab was the second PD-1 antibody to achieve accelerated approval and breakthrough therapy status by the U.S. Food and Drug Administration (FDA), providing an option for individuals with late-stage cancer who have been through several other therapies and yet still have disease progression. The FDA approved nivolumab (as a single agent) for the treatment of unresectable or metastatic melanoma and disease progression in individuals following ipilimumab (Yervoy™ intravenous [IV]) and, if BRAF V600 mutation positive, a BRAF inhibitor. BRAF inhibitors are dabrafenib (Tafinlar® oral) or vemurafenib (Zelboraf® oral).

The FDA accelerated approval of nivolumab was based on preliminary data from the CheckMate 037 trial. Continued approval of nivolumab is contingent on confirmatory trials underway. The single-arm, open-label, multicenter phase III trial randomized subjects 2:1 to nivolumab or chemotherapy (physician's option of dacarbazine or carboplatin and paclitaxel). All subjects had disease progression following ipilimumab and a BRAF inhibitor, if the V600 mutation was positive. The preliminary data reported 120 subjects (median age 59.5 years) with unresectable or metastatic melanoma with disease progression within 24 weeks of their last dose of ipilimumab, and if BRAF V600 mutation positive, prior treatment with BRAF inhibitor. An overall response rate (ORR) was achieved in 32% of nivolumab subjects; of the 38 subjects with responses, 33 had duration from 2.6-10 months (13 subjects had response of 6 months or more). The trial excluded participants with prior treatment with another PD-1 agent, known autoimmune disease, an unstable chronic condition requiring corticosteroids or other immunosuppressive medication and active hepatitis B, hepatitis C or a history of HIV. The most common drug related adverse events reported were rash (21%), itching (19%), cough (17%), upper respiratory tract infections (11%), and peripheral edema (10%).

In 2015, Robert and colleagues reported on the results of the phase III CheckMate-066 trial of 418 participants (adults 18 years or older) with unresectable, untreated stage III or IV metastatic melanoma (per American Joint Committee of Cancer [AJCC] staging system) without a BRAF mutation. Participants were randomly assigned to receive nivolumab or dacarbazine. Additional inclusion criteria for the study included participants who had an ECOG score of 0 or 1 (on scale of 0 to 5). Major exclusion criteria included active brain or leptomeningeal metastases, uveal melanoma, and any active, known or suspected autoimmune disease. The 1-year overall survival

(OS) was 72.9% with nivolumab versus 42.1% for chemotherapy group (hazard ratio [HR]=0.42; p<0.001). The median progression-free survival (PFS) was 5.1 months versus 2.2 months, for nivolumab and dacarbazine, respectively. The safety profiles were similar between groups with treatment well tolerated in this population. There were no drug–related deaths reported. Grade 3 or 4 adverse events occurred in 11.7% of study participants treated with nivolumab and 17.6% of participants treated with dacarbazine. Common adverse events associated with use of nivolumab were fatigue, pruritus, and nausea. The authors concluded, "nivolumab was associated with a significant improvement in overall survival and progression-free survival, as compared with dacarbazine. Nivolumab was associated with a low risk of high-grade toxicity effects."

The FDA expanded indication for combination use of nivolumab and ipilimumab as treatment of individuals with BRAF V600 wild-type unresectable or metastatic melanoma are based on findings from the Phase II Check-Mate-069 study. The double-blind trial with 142 treatment-naïve participants with stage III/IV melanoma were randomized in a 2:1 ratio to receive ipilimumab plus nivolumab (n=95) or ipilimumab monotherapy (n=47) until disease progression or death. The rate of confirmed objective response among participants with BRAF V600 wild-type tumors was 61% (44 of 72 participants) in the group that received combination therapy versus 11% (4 of 37 participants) in the ipilimumab monotherapy group (p<0.001). In summary the authors reported that:

> The combination of ipilimumab plus nivolumab resulted in durable responses and substantially higher objective response rate, longer progression-free survival, and higher rates of complete response than ipilimumab monotherapy among patients with BRAF wild-type advanced melanoma and those with BRAF-mutant advanced melanoma. The incidence of grade 3 or 4 adverse events was higher with combination therapy, but adverse events were generally manageable when established safety guidelines were used. The risk-benefit profile of combined PD-1 and CTLA-4 blockade, as compared with monotherapy, will be further clarified by data from ongoing phase 3 double-blind trials.

Larkin and colleagues (2015) reported results from the CheckMate 067 trial, a randomized, double-blind phase 3 study that assigned 945 treatment naïve participants with histologically confirmed stage III (unresectable) or IV metastatic melanoma to receive nivolumab alone (n=316), nivolumab plus ipilimumab (n=314), or ipilimumab alone (n=315). Additional inclusion criteria included adults age 18 years or older; ECOG score 0 or 1; BRAF V600 mutation status, and measurable disease by computed tomography (CT) or magnetic resonance imaging (MRI) per RECIST 1.1 criteria. Key exclusion criteria included presence of autoimmune disease, active brain metastases or ocular melanoma, condition requiring systemic treatment with either corticosteroids or other immunosuppressive medications and prior treatment with another PD-1 agent. Co-primary endpoints were PFS and OS.

The median progression-free survival was 11.5 months (95% confidence interval [CI], 8.9 to 16.7) with nivolumab plus ipilimumab, as compared with 2.9 months (95% CI, 2.8 to 3.4) with ipilimumab (hazard ratio for death or disease progression, 0.42; 99.5% CI, 0.31 to 0.57; P<0.001) and 6.9 months (95% CI, 4.3 to 9.5) with nivolumab (hazard ratio for the comparison with ipilimumab, 0.57; 99.5% CI, 0.43 to 0.76; P<0.001). In patients with tumors positive for the PD-1 ligand (PD-L1), the median progression-free survival was 14.0 months in the nivolumab-

plus-ipilimumab group and in the nivolumab group, but in patients with PD-L1-negative tumors, progression-free survival was longer with the combination therapy than with nivolumab alone (11.2 months [95% CI, 8.0 to not reached] vs. 5.3 months [95% CI, 2.8 to 7.1]). Treatment-related adverse events of grade 3 or 4 occurred in 16.3% of the patients in the nivolumab group, 55.0% of those in the nivolumab-plus-ipilimumab group, and 27.3% of those in the ipilimumab group.

In conclusion the authors found individuals with previously untreated advanced melanoma had longer PFS and higher rates of OS with nivolumab alone and with combination of nivolumab and ipilimumab than with ipilimumab alone.

The updated NCCN Drugs and Biologics Compendium™ and the NCCN clinical practice guideline (CPG) in melanoma (2018) include a category 1 recommendations for use of nivolumab as a single agent or combination with ipilimumab as first-line therapy. Second-line or subsequent therapy for treatment of metastatic or unresectable melanoma has a 2A recommendation. The NCCN off-label recommendation is based on a phase III trial of nivolumab/ipilimumab or nivolumab monotherapy versus ipilimumab monotherapy was conducted in previously untreated patients with unresectable stage II or IV melanoma. The NCCN CPG for melanoma includes a Category 1 recommendation for the use of nivolumab in the treatment of adjuvant treatment for resected stage IIIB/C melanoma (preferred adjuvant immunotherapy regimen). "Nivolumab has shown a clinically significant improvement in relapse free survival (RFS) compared to high-dose ipilimumab, but its impact on overall survival (OS) has not yet been reported. Most panel members prefer adjuvant nivolumab over high-dose ipilimumab based on improved efficacy and less toxicity, even in the absence of reported OS data."

Weber and colleagues (2017) reported results from the CheckMate 238 study, a randomized, double-blind, phase III trial that randomly assigned 906 participants who were undergoing complete resection of stage IIIB, IIIC, or IV melanoma and received adjuvant nivolumab or ipilimumab up to one year or until disease recurrence, or until disease recurrence, unacceptable toxic effects or withdrawal of consent. The authors reported:

> A minimum follow-up of 18 months, the 12-month rate of recurrence-free survival was 70.5% (95% confidence interval [CI], 66.1 to 74.5) in the nivolumab group and 60.8% (95% CI, 56.0 to 65.2) in the ipilimumab group (hazard ratio for disease recurrence or death, 0.65; 97.56% CI, 0.51 to 0.83; P<0.001). Treatment-related grade 3 or 4 adverse events were reported in 14.4% of the patients in the nivolumab group and in 45.9% of those in the ipilimumab group; treatment was discontinued because of any adverse event in 9.7% and 42.6% of the patients, respectively. Two deaths (0.4%) related to toxic effects were reported in the ipilimumab group more than 100 days after treatment.

In conclusion, individuals undergoing resection for stage IIIB, IIIC or IV melanoma, adjuvant therapy with nivolumab resulted in a longer recurrent-free survival and lower rate of grade 3 or 4 adverse events than adjuvant treatment with ipilimumab.

Primary ocular melanoma is treated with radiation, enucleation (eye removal) or transscleral resection depending on the size and location of the tumor.

Non-Small Cell Lung Cancer (NSCLC)
Lung cancer is the leading cause of death in the United States, with only 16.8% of patients surviving five or more years after diagnosis. The primary risk factor for lung cancer is smoking tobacco. Non-small cell lung cancer (NSCLC) accounts for more than 85% of all lung cancer cases. The two major types of NSCLC are non-squamous carcinoma and squamous cell (epidermoid) carcinoma.

On March 4, 2015, the FDA expanded the indication for nivolumab to include treatment of individuals with metastatic squamous NSCLC with progression on or after platinum-based chemotherapy. On October 9, 2015, the FDA granted accelerated approval for nivolumab to treat individuals with advanced (metastatic) NSCLC whose disease progressed during or after platinum-based chemotherapy.

The FDA expanded use for metastatic squamous NSCLC was based on superior OS from the CheckMate-017 trial. This open-label, multicenter, multinational randomized trial allocated participants who had experienced disease progression while on or after receiving a platinum-based chemotherapy regimen to nivolumab (n=135) or docetaxel (n=137). Nivolumab demonstrated improvement in OS as compared with docetaxel, with median OS of 9.2 months (95% CI: 7.3, 13.3) for nivolumab population and 6 months (95% CI: 5.1, 7.3) for docetaxel (HR 0.59% CI: 0.44, 0.79, p=0.00025).

Rizvi and colleagues (2015) reported results from the CheckMate-063 study, a phase II single-arm, multicenter international study of participants with metastatic squamous NSCLC who had disease progression after platinum-based therapy and at least one systemic regimen. A total of 117 participants received IV nivolumab (3 mg/kg) treatment every 2 weeks until disease progression or complications related to drug toxicity. The major efficacy outcome was based on OS of participants with confirmed objective response, as assessed by an independent radiology review committee (IRC) using Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1).

> Median time to response was 3.3 months (IQR 2.2-4.8). and median duration of response was not reached (95% CI 8.31-not applicable); 13 (77%) of 17 of responses were ongoing at the time of analysis. 30 (26%) of 117 patients had stable disease (median duration 6.0 months, 95% CI 4.7-10.9). 20 (17%) of 117 patients reported grade 3-4 treatment related adverse events, including: fatigue (five [4%] of 117 patients), pneumonitis (four [3%]), and diarrhea (three [3%]). There were two treatment associated deaths caused by pneumonia and ischemic stroke that occurred in patients with multiple comorbidities in the setting of progressive disease.

Few treatment options exist for advanced, refractory squamous non-small-cell lung cancer, with no clear standard of care. Our study shows clinically meaningful activity and a manageable safety profile of nivolumab for this patient population and supports assessment of nivolumab in phase 3 studies of first-line and second-line treatment.

In the non-small cell lung cancer CPG in oncology (2017), the NCCN panel offers a category 1 recommendation for use of nivolumab:

> As subsequent therapy for patients with metastatic squamous cell carcinoma who have progressed on or after platinum-based chemotherapy based on data from a phase III randomized trial (CheckMate-017), the recent FDA approval, and results of a phase II trial. In an interim update, the NCCN Panel recommends nivolumab as subsequent therapy for patients with metastatic nonsquamous NSCLC who have progressed on or after platinum-based chemotherapy based on preliminary data from a phase III randomized trial (CheckMate-057). For patients receiving nivolumab, median overall survival was 12.2 months compared with 9.4 moths with docetaxel (HR 0.73, 95% CI, 0.59 to 0.89; P=.0015). Fewer grade 3 to 5 adverse events were reported for nivolumab (10%) when compared with docetaxel (54%) in the CheckMate-057 trial. Although many patients with metastatic nonsquamous NSCLC benefit from nivolumab, those whose tumors have PD-L1 staining of 1% to 10% or more have overall survival of 17.2 to 19.4 months compared with 8 to 9 months for docetaxel. However, the NCCN Panel does not recommend testing for PD-L1, because many patients with metastatic NSCLC benefit from nivolumab.

Renal Cell Carcinoma
On November 23, 2015, the FDA expanded the use of nivolumab for treatment of individuals with advanced (metastatic) renal cell carcinoma who have received prior anti-angiogenic therapy, based on results from the CheckMate-025 trial. Motzer and colleagues reported results from the CheckMate-025 trial, a randomized, open-label, phase 3 study that compared nivolumab with everolimus. A total of 821 participants with advanced (clear cell) RCC were randomized in a 1:1 ratio to receive nivolumab 3 mg per kilogram intravenously every 2 weeks or 10 mg of everolimus administered orally daily. The primary endpoint for the study was OS; the median OS for the nivolumab group was 25.0 months (95% CI, 21.8 to not estimable) versus19.6 months (95% CI, 17.6 to 23.1) for the everolimus group. "The hazard ratio for death with nivolumab versus everolimus was 0.73 (98.5% CI, 0.57 to 0.93; P=0.002), which met the prespecified criterion for superiority (P≤0.0148)". Fewer grade 3 or 4 adverse events were reported in the nivolumab group with adverse events occurring in 19% of the nivolumab population compared to 37% of the everolimus population.

The NCCN Drugs and Biologics Compendium™ (2017) and the NCCN CPG for kidney cancer included a category 1 recommendation for the use of nivolumab as subsequent therapy as a single agent in treatment of individuals with clear cell histology after tyrosine kinase inhibitor therapy based on results from the CheckMate-025 trial reported by Motzer and colleagues. The NCCN CPG (2017) includes a 2A recommendation for the use of nivolumab as systemic therapy for non-clear cell histology.

Hodgkin Lymphoma, Classical
On May 17, 2016, the U. S. Food and Drug Administration granted accelerated approval to nivolumab for the treatment of patients with classical Hodgkin lymphoma (cHL) that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and post-transplantation brentuximab vedotin (Adcetris).

The NCCN Drugs and Biologics Compendium and the NCCN CPG for Hodgkin disease (2017) included a 2A recommendation for off-label use of nivolumab as an additional therapy option when used as a single agent for individuals with relapsed or refractory cHL. The recommendation is based on uniform consensus and data from a phase I clinical trial abstract. Ansell and colleagues (2015) reported preliminary findings of a study of 23 participants with relapsed or refractory Hodgkin lymphoma that were heavily pretreated, who received nivolumab every 2 weeks until they had a complete response (CR), tumor progression or excessive toxic effects from the medication. Twenty participants (87%) achieved an objective response, including a CR in 17% of participants and 70% with a partial response; the remaining 13% (n=3) had stable disease. At 24 weeks, the rate of progression-free survival was 86%; 11 subjects continued to participate in the study, 6 dropped out due to stem cell transplant, 4 due to disease progression and the remaining 2 due to drug toxicity. The authors concluded that "Nivolumab has substantial therapeutic activity and an acceptable safety profile in patients with previously heavily treated relapsed or refractory Hodgkin's lymphoma." Updated results were also reported in an abstract by Timmerman (2015). The author concluded that:

> In Hodgkin lymphoma patients, the CR rate was 26% with a PR in 61% and stable disease in 13%. In Hodgkin lymphoma patients, the median duration of response was not reached (range, 2 to 91+ months) after a median follow-up of 86 weeks. Responses were ongoing in 50%. Median PFS for Hodgkin lymphoma patients was 92.1 weeks.

Small Cell Lung Cancer

Neuroendocrine tumors account for approximately 20% of lung cancers, most are small cell lung cancer (SCLC). In 2016, an estimated 31,000 new cases of SCLC will occur in the United States. SCLC is characterized by a rapid doubling time, high growth fraction, and early development of widespread metastases. Most patients with SCLC present with hematogenous metastases; approximately one third present with limited disease confined to the chest. SCLC is highly sensitive to initial chemotherapy and radiotherapy; however, most patients eventually die of recurrent disease.

The NCCN Drug and Biologics Compendium (2017) lists nivolumab for small cell lung cancer as subsequent systemic therapy for patients with performance status 0-2 as a single agent or in combination with ipilimumab for relapse within 6 months following complete or partial response or stable disease with initial treatment, or for primary progressive disease.

Antonia, et al. assessed safety and activity of nivolumab and nivolumab plus ipilimumab in patients with small cell lung cancer (SCLC) who progressed after one or more previous regimens. The SCLC cohort of this phase 1/2 multicenter, multi-arm, open-label trial was conducted at 23 sites (academic centers and hospitals) in six countries. Eligible patients were 18 years of age or older, had limited-stage or extensive-stage SCLC, and had disease progression after at least one previous platinum-containing regimen. Patients received nivolumab (3 mg/kg bodyweight intravenously) every 2 weeks (given until disease progression or unacceptable toxicity), or nivolumab plus ipilimumab (1 mg/kg plus 1 mg/kg, 1 mg/kg plus 3 mg/kg, or 3 mg/kg plus 1 mg/kg, intravenously) every 3 weeks for four cycles, followed by nivolumab 3 mg/kg every 2 weeks. Patients were either assigned to nivolumab monotherapy or assessed in a

dose-escalating safety phase for the nivolumab/ipilimumab combination beginning at nivolumab 1 mg/kg plus ipilimumab 1 mg/kg. Depending on tolerability, patients were then assigned to nivolumab 1 mg/kg plus ipilimumab 3 mg/kg or nivolumab 3 mg/kg plus ipilimumab 1 mg/kg. The primary endpoint was objective response by investigator assessment. All analyses included patients who were enrolled at least 90 days before database lock. Between Nov 18, 2013, and July 28, 2015, 216 patients were enrolled and treated (98 with nivolumab 3 mg/kg, three with nivolumab 1 mg/kg plus ipilimumab 1 mg/kg, 61 with nivolumab 1 mg/kg plus ipilimumab 3 mg/kg, and 54 with nivolumab 3 mg/kg plus ipilimumab 1 mg/kg). At database lock on Nov 6, 2015, median follow-up for patients continuing in the study (including those who had died or discontinued treatment) was 198·5 days (IQR 163·0-464·0) for nivolumab 3 mg/kg, 302 days 1(IQR not calculable) for nivolumab 1 mg/kg plus ipilimumab 1 mg/kg, 361·0 days (273·0-470·0) for nivolumab 1 mg/kg plus ipilimumab 3 mg/kg, and 260·5 days (248·0-288·0) for nivolumab 3 mg/kg plus ipilimumab 1 mg/kg. An objective response was achieved in ten (10%) of 98 patients receiving nivolumab 3 mg/kg, one (33%) of three patients receiving nivolumab 1 mg/kg plus ipilimumab 1 mg/kg, 14 (23%) of 61 receiving nivolumab 1 mg/kg plus ipilimumab 3 mg/kg, and ten (19%) of 54 receiving nivolumab 3 mg/kg plus ipilimumab 1 mg/kg. Grade 3 or 4 treatment-related adverse events occurred in 13 (13%) patients in the nivolumab 3 mg/kg cohort, 18 (30%) in the nivolumab 1 mg/kg plus ipilimumab 3 mg/kg cohort, and ten (19%) in the nivolumab 3 mg/kg plus ipilimumab 1 mg/kg cohort; the most commonly reported grade 3 or 4 treatment-related adverse events were increased lipase (none vs 5 [8%] vs none) and diarrhea (none vs 3 [5%] vs 1 [2%]). No patients in the nivolumab 1 mg/kg plus ipilimumab 1 mg/kg cohort had a grade 3 or 4 treatment-related adverse event. Six (6%) patients in the nivolumab 3 mg/kg group, seven (11%) in the nivolumab 1 mg/kg plus ipilimumab 3 mg/kg group, and four (7%) in the nivolumab 3 mg/kg plus ipilimumab 1 mg/kg group discontinued treatment due to treatment-related adverse events. Two patients who received nivolumab 1 mg/kg plus ipilimumab 3 mg/kg died from treatment-related adverse events (myasthenia gravis and worsening of renal failure), and one patient who received nivolumab 3 mg/kg plus ipilimumab 1 mg/kg died from treatment-related pneumonitis. The investigators stated that these data support the evaluation of nivolumab and nivolumab plus ipilimumab in phase 3 randomized controlled trials in SCLC.

Squamous Cell Carcinoma of the Head and Neck

On November 10, 2016, Bristol-Myers Squibb Company received FDA accelerated approval for use of nivolumab for the treatment of recurrent or metastatic SCCHN with disease progression on or after platinum-based therapy. The FDA approval was based on preliminary findings reported by Ferris and colleagues from the CheckMate-0141 trial, an open-label Phase III trial comparing nivolumab to investigators choice chemotherapy. The NCCN Drugs and Biologics Compendium and the NCCN CPG in Oncology on head and neck cancer (2016) included a category 1 recommendation for off-label use of nivolumab in treatment of recurrent, unresectable or metastatic SCCHN, as a single agent with disease progression on or after platinum-containing chemotherapy. The recommendations are based on interim results from the CheckMate-141 trial that randomly assigned participants at a 2:1 ratio to receive intravenous nivolumab or a standard, single-agent systemic therapy (methotrexate, docetaxel, or cetuximab). Primary end point was overall survival, defined as the time from randomization to the date of death from any cause. Ferris and colleagues reported findings:

> The median overall survival was 7.5 months (95% confidence interval [CI], 5.5 to 9.1) in the nivolumab group versus 5.1 months (95% CI, 4.0 to 6.0) in the standard-therapy group. Overall survival was significantly longer with nivolumab than with standard therapy, and nivolumab treated patients had a risk of death that was 30% lower than the risk among patients assigned to standard therapy (hazard ratio, 0.70; 97.73% CI, 0.51 to 0.96; P=0.01). In conclusion, nivolumab prolonged survival, as compared with standard therapy, among patients with platinum-refractory squamous-cell carcinoma of the head and neck. Nivolumab was associated with fewer toxic effects of grade 3 or 4 than standard therapy (13.1% vs. 35.1%) and with maintenance of quality of life among patients with a treatment-refractory cancer that otherwise has serious adverse effects on quality of life as it leads to death.

Urothelial Carcinoma
On February 2, 2017, Bristol-Myers Squibb Company received FDA accelerated approval for use of nivolumab for the treatment of locally advanced or metastatic urothelial carcinoma with disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with a platinum-containing chemotherapy. The FDA approval was based on interim results from the CheckMate 275 trial, a multicenter, single-arm, phase 2 study that evaluated effectiveness of nivolumab in 270 participants (18 years or older) with metastatic or surgically unresectable locally advanced urothelial carcinoma. The primary endpoint was an objective response (OR) in participants treated with nivolumab and PD-L1 expression (≥ 5% and ≥ 1%). Sharma and colleagues (2017) reported the following findings:

> Confirmed objective response was achieved in 52 (19.6%, 95% CI 15.0-24.9) patients. Confirmed objective response was achieved in 23 (28.4%, 95% CI 18.9-39.5) of the 81 patients with PD-L1 expression of 5% or greater, 29 (23.8%, 95% CI 16.5-32.3) of the 122 patients with PD-L1 expression of 1% or greater, and 23 (16.1%, 95% CI 10.5-23.1) of the 143 patients with PD-L1 expression of less than 1%.

The authors identified no new safety concerns with use of nivolumab monotherapy. Treatment-related adverse events occurred in 174 (64%) of 270 participants. Fatigue was the most common treatment-related event of any grade, reported in 17% (n=45) of participants. 48 (18%) had grade 3 or 4 treatment-related events, most commonly diarrhea and fatigue. The authors concluded that "in view of the scarcity of treatment options and high unmet medical need in this patient population, these data support the use of nivolumab as a new treatment option if platinum-based chemotherapy is unsuccessful."

Colorectal Cancer:
On July 31, 2017, the FDA expanded approval of nivolumab in the treatment of adults or adolescents (12 years or older) with MSI-H or dMMR metastatic colorectal cancer that has progressed following prior treatment with fluoropyrimidine, oxaliplatin, and irinotecan (n=53). The FDA approval was based on unpublished data from the CheckMate 142 study which demonstrated an objective response rate in 28% (95% CI: 17-42; 15/53) among participant who received prior treatment (fluoropyrimidine, oxaliplatin, and irinotecan).

In March 2017, the NCCN Drugs and Biologics Compendium and the NCCN CPG in Oncology on colon cancer and rectal cancer lists off-label use of nivolumab for individuals with unresectable metachronous metastases or unresectable advanced or metastatic colorectal cancer. The recommendations were based on 2A category of evidence and uniform consensus. The panel recommends:

> Use of pembrolizumab or nivolumab as treatment options in patients with metastatic MMR-deficient colorectal cancer in second- or third-line therapy. Patients progressing on either of these drugs should not be offered the other. Additional clinical trials are ongoing to confirm the benefit of these drugs in this setting.

Hepatocellular Carcinoma
On September 22, 2017, Bristol-Myers Squibb Company received FDA accelerated approval for use of nivolumab for the treatment of individuals with advanced hepatocellular carcinoma who have been previously treated with sorafenib. The FDA approval was based unpublished data from the CheckMate 040 trial, a phase 1/ 2 open-label pivotal study that evaluated tumor response rate and durability of nivolumab in participants with advanced hepatocellular carcinoma who progressed on or were intolerant to sorafenib. In the CheckMate -040 trial, nivolumab was evaluated in a subgroup of 154 participants, 14.3% (95% CI: 9.2-20.8; 22/154) of participants responded to treatment with nivolumab, 3 (1.9%) participants had a complete response and 12.3% of participants (n=19) had a partial response. Of the 22 participants that responded to treatment, the responses ranged from 3.2 to 38.2+ months; 91% of those participants had responses of six months or longer and 55% had responses of 12 months or longer.

Merkel Cell Carcinoma:
In the NCCN Drugs and Biologics Compendium and the NCCN CPG in Oncology on Merkel cell carcinoma (2017), the panel included a category 2A recommendation for off-label use of nivolumab in the treatment of disseminated disease as clinical judgment dictates; the "preliminary data from non-randomized trials in patients with MCC demonstrate that rates of durable response are improved with PD-1/PD-L1 blockage compared with cytotoxic therapy".

Malignant Pleural Mesothelioma:
The recently updated NCCN CPG for malignant pleural mesothelioma (2017) includes a category 2A recommendation for use of nivolumab (immunotherapy) as subsequent systemic therapy for the treatment of malignant pleural mesothelioma (MPM), a highly aggressive cancer with poor prognosis and limited treatment options. The NCCN recommendation is based on preliminary results of the IFCT-1501 MAPS2 randomized phase II trial, an ongoing study evaluating second or third-line nivolumab versus nivolumab plus ipilimumab in MPM. There were more reported grade 3 & 4 toxicities in the combination arm (86.9%/ 16.4%) versus the nivolumab arm (77.8%/ 9.5%); there were 3 treatment related deaths reported in the combination arm (1 metabolic encephalopathy, 1 fulminant hepatitis, 1 acute renal failure). The authors concluded that immunotherapy may provide new options for individuals with MPM.

Key Words:

Metastatic melanoma, Non-small cell lung cancer (NSCLC), pembrolizumab, Opdivo, nivolumab, Yervoy, ipilimumab, renal cell carcinoma, Hodgkin lymphoma, Keytruda, small cell lung cancer, SCLC, bladder cancer, urothelial carcinoma, squamous cell carcinoma of head and neck, SCCHN, hepatocellular carcinoma, colon cancer, malignant pleural mesothelioma, Merkel cell carcinoma

Approved by Governing Bodies

On December 22, 2014, nivolumab received accelerated approval and breakthrough therapy status by the U.S. Food and Drug Administration (FDA), for the treatment of individuals with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

On March 4, 2015, the FDA granted approval to nivolumab for the treatment of individuals with metastatic squamous non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy.

On September 30, 2015, the FDA granted accelerated approval for nivolumab in combination with ipilimumab for the treatment of individuals with unresectable or metastatic melanoma BRAF V600 wild-type.

On October 9, 2015, the FDA approved nivolumab for the treatment of individuals with metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Opdivo.

On November 23, 2015, the FDA approved nivolumab for the treatment of advanced renal cell carcinoma in individuals who have received prior angiogenic therapy.

On January 23, 2016, the FDA expanded the use of nivolumab in combination with ipilimumab for the treatment of individuals with BRAF V600 wild-type and BRAF V600 mutation-positive unresectable or metastatic melanoma. The approval expands the original indication for combination therapy with nivolumab and ipilimumab regardless of BRAF mutation status based on results from the CheckMate-067 trial.

On May 17, 2016, the FDA granted accelerated approval to nivolumab for the treatment of individuals with classical Hodgkin lymphoma (cHL) that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and post-transplantation brentuximab vedotin.

On November 10, 2016, the FDA approved nivolumab for the treatment of individuals with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) with disease progression on or after platinum-based therapy.

On February 2, 2017, the FDA approved nivolumab for the treatment of individuals with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or have progression within 12 months of neoadjuvant treatment with a platinum-containing chemotherapy.

On July 31, 2017, the FDA granted accelerated approval to nivolumab for the treatment of patients 12 years and older with mismatch repair deficient (dMMR) and microsatellite instability high (MSI-H) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

On September 22, 2017, the FDA granted accelerated approval to nivolumab for the treatment of hepatocellular carcinoma (HCC) in patients who have been previously treated with sorafenib.

On December 20, 2017, the FDA granted regular approval of the anti-PD 1 monoclonal antibody, nivolumab for the adjuvant treatment of patients with melanoma with involvement of lymph nodes or in patients with metastatic disease who have undergone complete resection. Nivolumab was previously approved for the treatment of patients with unresectable or metastatic melanoma.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

Current Coding:

CPT Codes:

J9299	Injection, nivolumab, 1 mg

References:

1. American Cancer Society. www.cancer.org/cancer/skincancer-melanoma/detailedguide/melanoma-skin-cancer-key-statistics.
2. Ansell SM, Lesokhin AM, Borrello I, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N Engl J Med. 2015; 372(4):311-319.
3. Antonia SJ, Lopez-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicenter, open-label, phase 1/2 trial. Lancet Oncol. 2016; 17:883-895.
4. Arkenau HT, Kefford R, Long GV. Targeting BRAF for patients with melanoma. Br J Cancer. 2011; 104(3):392-398.
5. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small cell lung cancer. N Eng J Med. 2015; 373(17):1627-1639.
6. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med. 2015; 373(2):123-135.

7. Bristol-Myers Squibb. A study to compare BMS-936558 to the physician's choice of either dacarbazine or carboplatin and paclitaxel in advanced melanoma patients that have progressed following anti-CTLA-4 therapy (CheckMate 037). NLM Identifier: NCT01721746. Last updated September 26, 2017. Available at: www.clinicaltrials.gov/ct2/show/NCT01721746?term=Checkmate+037&rank=1.
8. Bristol-Myers Squibb. A study of nivolumab in participants with metastatic or unresectable bladder cancer. NLM Identifier: NCT02387996. Last updated July 11, 2017. Available at: www.clinicaltrials.gov/ct2/show/NCT02387996.
9. Bristol-Myers Squibb. An immune-therapy study to evaluate the effectiveness, safety and tolerability of nivolumab or nivolumab in combination with other agents in patients with advanced liver cancer. (CheckMate 040). NLM Identifier: NLM Identifier: NCT01658878. Last updated September 28, 2017. Available at: www.clinicaltrials.gov/ct2/show/NCT01658878
10. Bristol-Myers Squibb. An investigational immune-therapy study of nivolumab, and nivolumab with other anti-cancer drugs, in colon cancer that has come back or has spread (CheckMate 142). NLM Identifier: NCT02060188. Last updated September 18, 2017. Available at: www.clinicaltrials.gov/ct2/show/NCT02060188.
11. Bristol-Myers Squibb. Phase 2, randomized, double blinded, study of nivolumab (BMS-936558) in combination with ipilimumab vs ipilimumab alone in subjects with previously untreated, unresectable or metastatic melanoma (CheckMate 069). NLM Identifier: NCT01927419. Last updated September 29, 2016. Available at: www.clinicaltrials.gov/ct2/show/NCT01927419?term=checkmate+069&rank=1.
12. Bristol-Myers Squibb. Phase 3 study of nivolumab or nivolumab plus ipilimumab versus ipilimumab alone in previously untreated advanced melanoma (CheckMate 067). NLM Identifier: NCT01844505. Last updated September 29, 2016. Available at: www.clinicaltrials.gov/ct2/show/NCT01844505.
13. Bristol-Myers Squibb. Safety study of nivolumab by itself or in combination with ipilimumab or in combination with lirilumab in patients with lymphoma and multiple myeloma. NLM Identifier: NCT01592370. Last updated September 6, 2017. Available at: www.clinicaltrials.gov/ct2/show/NCT01592370.
14. Bristol-Myers Squibb. Study of BMS-936558 (nivolumab) compared to docetaxel in previously treated advanced or metastatic squamous cell non-small cell lung cancer (NSCLC) (CheckMate 017). NLM Identifier: NCT01642004. Last updated February 1, 2017. Available at: www.clinicaltrials.gov/ct2/show/NCT01642004?term=CheckMate-017&rank=1.
15. Bristol-Myers Squibb. Study of BMS-936558 vs. dacarbazine in untreated, unresectable or metastatic melanoma (CheckMate 066). NLM Identifier: NCT01721772. Last updated July 11, 2017. Available at: www.clinicaltrials.gov/ct2/show/NCT01721772?term=Checkmate+066&rank=1.
16. Bristol-Myers Squibb. Study of nivolumab (BMS-936558) in subjects with advanced or metastatic squamous cell non-small cell lung cancer who have received at least two prior systemic regimens (CheckMate 063). NLM Identifier: NCT01721759. Last updated September 8, 2017. Available at: www.clinicaltrials.gov/ct2/show/NCT01721759?term=Checkmate+063&rank=1.
17. Bristol-Myers Squibb. Study of nivolumab (BMS-936558) in subjects with advanced or metastatic squamous cell non-small cell lung cancer who have received at least two prior

systemic regimens (CheckMate 063). NLM Identifier: NCT01721759. Available at: www.clinicaltrials.gov/ct2/show/NCT01721759?term=Checkmate+063&rank=1.
18. Chapman PB, Hauschild A, Sondak VK. Frontline Approach to Metastatic BRAF-Mutant Melanoma Diagnosis, Molecular Evaluation, and Treatment Choice. Asco.org/edbook.
19. Davies H, Bignell GR, Cox C, et al. Mutations of the BRAF gene in human cancer. Nature. 2002; 417(6892):949-954.
20. Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: globocan.iarc.fr.
21. Ferris RL, Blumenschein G, Fayette J et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. N Engl J Med. 2016; 375:1856-1867.
22. Flaherty KT, Puzanov I, Kim KB, et al. Inhibition of mutated, activated BRAF in metastatic melanoma. N Engl J Med. 2010; 363(9):809-819.
23. Hamanishi J, Mandai M, Ikeda T, et al. Safety and autitumor activity of anti-PD-1 antibody, nivolumab, in patients with platinum-resistant ovarian cancer. J Clin Oncol. 2015; 33(34):4015-4022.
24. Khan MA, Andrews S, Ismail-Khan R, et al. Overall and progression-free survival in metastatic melanoma: analysis of a single-institution database. Cancer Control. 2006; 13(3):211-217.
25. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med. 2015; 373(1):23-34.
26. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med. 2015; 373(19):1803-1813.
27. National Cancer Institute. Common terminology criteria for adverse events. Version 4.03. June 2010. Available at: www.evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.
28. National Comprehensive Cancer Network®. NCCN Drugs & Biologic Compendium™ (electronic version). For additional information visit the NCCN website: www.nccn.org
29. National Comprehensive Cancer Network® NCCN Clinical Practice Guidelines in Oncology. Bladder Cancer. Version 1.2018. Available at: www.nccn.org.
30. NCCN Clinical Practice Guidelines in Oncology. Colon Cancer. Version 1.2018. Available at: www.nccn.org.
31. NCCN Clinical Practice Guidelines in Oncology. Hepatobiliary Cancers. Version 4.2017. Available at: www.nccn.org.
32. NCCN Clinical Practice Guidelines in Oncology. Hodgkin Lymphoma. Version 1.2018. Available at: www.nccn.org.
33. NCCN Clinical Practice Guidelines in Oncology. Kidney Cancer. Version 2.2018. Available at: www.nccn.org.
34. NCCN Clinical Practice Guidelines in Oncology. Melanoma. Version 2.2018. Available at: www. nccn.org.
35. NCCN Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer. Version 2.2018. Available at: www.nccn.org.
36. NCCN Clinical Practice Guidelines in Oncology. Malignant Pleural Mesothelioma. Version 2.2017. Available at: www.nccn.org.
37. NCCN Clinical Practice Guidelines in Oncology. Merkel Cell Carcinoma. Version 2.2017. Available at: www.nccn.org.

38. NCCN Clinical Practice Guidelines in Oncology. Rectal Cancer. Version 2.2017. Available at: www.nccn.org.
39. NCCN Clinical Practice Guidelines in Oncology. Small Cell Lung Cancer. Version2.2018. Available at: www.nccn.org.
40. NCCN Clinical Practice Guidelines in Oncology. Head and Neck Cancer. Version 2.2017. Available at: www.nccn.org.
41. NCCN Categories of Evidence and Consensus. Available at: //www.nccn.org/professionals/physician_gls/categories_of_consensus.asp.
42. Nivolumab. Clinicaltrials.gov. Available at www.clinicaltrials.gov/ct2/results?term=nivolumab. February 2015.
43. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative oncology Group. Am J Clin Oncol. 1982; 5(6):649-655.
44. Opdivo prescribing information. Bristol-Myers Squibb Company. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2015/125527s000lbl.pdf
45. Overman MJ, McDermott R, Leach JL, et al. Nivolumab in patients with metastatic DNA mismatch repair- deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicenter, phase 2 study. Lancet Oncolo. 2017; 18:1182-1191.
46. Postow MA, Chesney J, Pavlick AC, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N Eng J Med. 2015; 372(21):2006-2017.
47. Rizvi NA, Mazieres J, Planchard D, et al. Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (CheckMate 063): a phase 2, single-arm trial. Lancet Oncol. 2015; 16(3):257-265.
48. Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med. 2015; 372(4):320-330.
49. Scherpereel A, Mazleres J, Greillier L, et al. Second- or third-line nivolumab (Nivo) versus nivo plus iplilimumab (Ipi) in malignant pleural mesothelioma (MPM) patients: Results of the IFCT-1501 MAPS2 randomized phase II trial. 2017; 35(18) [Epub Ahead of Print].
50. Shahabi V, Whitney G, Hamid O, et al. Assessment of association between BRAF-V600E mutation status in melanomas and clinical response to ipilimumab. Cancer Immunol Immunother. 2012; 61(5):733-737.
51. Sharma P, Retz M, Siefker-Radtke A, et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): A multicentre, single-arm, phase 2 trial. Lancet Oncol 2017.
52. Timmerman J, Armand P, Lesokhin AM, et al. Nivolumab in patients with relapsed or refractory lymphoid malignancies and classical Hodgkin lymphoma: Updated results of a phase 1 study (CA 209-039) [abstract]. Hematol Oncol. 2015; 33.
53. Topalian SL, Sznol M, McDermott DF, et al. Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. J Clin Oncol. 2014; 32(10):1020-1030.
54. Treatment of primary ocular melanoma. Available at: www.cancer.gov/cancertopics/pdq/treatment/intraocularmelanoma/HealthProfessional/page4.
55. Weber J, Mandala M, Del Vecchio M, et al. Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. N Eng J Med. 2017; doi:10.1059/NEJMoa1709030. [Epub ahead of print].

56. Weber JS, D'Angelo SP, Minor D, et al. nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate-037): a randomized, controlled, open-label, phase 3 trial. Lancet Oncol. 2015; 16(4):375-384.

Policy History

New policy created January 2015, effective date September 1, 2015
Medical Policy Group, September 2016
Available for comment September 23, 2016 to November 7, 2016.
Medical Policy Group, February 2017
Medical Policy Group, January 2018
Available for comment February 1, 2018 through March 18, 2018.
Medical Policy Group, November 2018