

## Corporate Medical Policy

### PD-1 Inhibitors

<b>File Name:</b>	pd_1_inhibitors
<b>Origination:</b>	9/2014
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<b>Last Review:</b>	8/2018

#### Description of Procedure or Service

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Programmed cell death protein 1, also known as PD-1 and CD279 (cluster of differentiation 279), is a protein that is encoded by the *PDCD1* gene.

PD-1, functioning as an immune checkpoint, plays an important role in down regulating the immune system by preventing the activation of T-cells, which in turn reduces autoimmunity and promotes self-tolerance. The inhibitory effect of PD-1 is accomplished through a dual mechanism of promoting apoptosis (programmed cell death) in antigen specific T-cells in lymph nodes while simultaneously reducing apoptosis in regulatory T cells (suppressor T cells).

A new class of drugs that block PD-1, the PD-1 inhibitors, activate the immune system to attack tumors and are indicated for the treatment of certain types of cancer.

Pembrolizumab (Keytruda<sup>®</sup>) is a humanized monoclonal antibody that blocks the interaction between PD-1 (programmed death receptor-1) and its ligands, PD-L1 (programmed death receptor-ligand 1) and PD-L2 (programmed death receptor-ligand 2), and may affect both tumor cells and healthy cells. In December 2015, the U.S. Food and Drug Administration approved pembrolizumab for the treatment of patients with unresectable or metastatic melanoma regardless of BRAF status. Pembrolizumab is also indicated as treatment for metastatic non-small cell lung cancer with progression on or after platinum-based chemotherapy. Other indications for pembrolizumab include treatment of recurrent or metastatic head and neck squamous cell cancer (HNSCC), relapsing or refractory classical Hodgkin lymphoma (cHL), refractory primary mediastinal large B-cell lymphoma (PMBCL), unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient solid tumors and colorectal cancer, recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma, and recurrent or metastatic cervical cancer.

Nivolumab (Opdivo<sup>®</sup>) is a human programmed death receptor-1 (PD-1) blocking antibody indicated for the treatment of patients with BRAF wild-type or BRAF mutation-positive unresectable or metastatic melanoma. On January 23, 2016, the U.S. Food and Drug Administration granted accelerated approval to nivolumab used in combination with ipilimumab for treatment of patients with unresectable or metastatic melanoma regardless of BRAF status; continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. On December 20, 2017, the U.S. Food and Drug Administration granted approval to nivolumab for the adjuvant treatment of patients with melanoma with lymph node involvement or in patients with metastatic disease who have undergone complete resection. Nivolumab (Opdivo) is also indicated as a treatment for advanced metastatic squamous non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy.

In November 2015, the U.S. Food and Drug Administration approved nivolumab for the treatment of patients with advanced (metastatic) renal cell carcinoma who have received prior anti-

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angiogenic therapy (treatments that interfere with the blood vessels that contribute to the growth of cancerous cells). Nivolumab is also approved, in combination with ipilimumab, to treat patients with intermediate or poor risk, previously untreated advanced renal cell carcinoma. Other indications for nivolumab include treatment of metastatic small cell lung cancer, classical Hodgkin lymphoma, recurrent or metastatic squamous cell carcinoma of the head and neck, metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient colorectal cancer, hepatocellular carcinoma in patients previously treated with sorafenib.

### Related Policies

BRAF Gene Mutation Testing to Select Melanoma Patients for BRAF Inhibitor Therapy  
Ipilimumab (Yervoy)

**\*\*\*Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

## Policy

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**BCBSNC will provide coverage for PD-1 Inhibitors when it is determined to be medically necessary because the medical criteria and guidelines noted below are met.**

## Benefits Application

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This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

## When PD-1 Inhibitors are covered

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Pembrolizumab (Keytruda) may be medically necessary when the following criteria are met:

1. The patient has unresectable or metastatic melanoma and pembrolizumab is used as monotherapy; **OR**
2. The patient has metastatic non-small cell lung cancer (NSCLC) with high PD-L1 tumor expression (Tumor Proportion Score or TPS  $\geq$  50%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, and no prior systemic chemotherapy treatment for metastatic NSCLC; **OR**
3. The patient has metastatic non-small cell lung cancer (NSCLC) with tumor expression of PD-L1 (TPS  $\geq$  1%) as determined by an FDA-approved test; **AND**
  - a. For the patient who has EGFR-mutation-positive or ALK-fusion oncogene-positive tumor, there is documentation of disease progression while on FDA-approved therapy for these mutations prior to receiving pembrolizumab (note: this does not apply if the patient's tumor does not have these mutations); **AND**
  - b. The patient has disease progression on or after platinum-based chemotherapy; **OR**
4. The patient has metastatic nonsquamous non-small cell lung cancer (NSCLC) and is receiving pembrolizumab as first-line treatment, in combination with pemetrexed and platinum chemotherapy; **OR**
5. The patient has unresectable or metastatic solid tumors with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) biomarkers who have progressed following prior treatment and have no alternative treatment options; **OR**

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6. The patient has colorectal cancer with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) biomarkers that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan; **OR**
7. The patient has recurrent or metastatic head and neck squamous cell cancer (HNSCC) with disease progression on or after platinum-containing chemotherapy; **OR**
8. The patient has locally advanced or metastatic urothelial carcinoma; **AND**
  - a. The patient is not eligible for cisplatin-containing chemotherapy and has PD-L1 tumor expression (Combined Positive Score or CPS  $\geq$  10) as determined by an FDA-approved test; **OR**
  - b. The patient is not eligible for any platinum-containing chemotherapy regardless of PD-L1 tumor expression status; **OR**
  - c. The patient has disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy; **OR**
9. The patient has classical Hodgkin lymphoma (cHL) that is refractory, or has relapsed after 3 or more prior lines of therapy; **OR**
10. The patient has recurrent or metastatic cervical cancer with disease progression on or after chemotherapy, and with PD-L1 tumor expression (CPS  $\geq$  1) as determined by an FDA-approved test; **OR**
11. The patient has primary mediastinal large B-cell lymphoma (PMBCL) that is refractory, or has relapsed following 2 or more prior lines of therapy, **AND** the patient does not require urgent cytoreductive therapy; **OR**
12. The patient has recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma with PD-L1 tumor expression (CPS  $\geq$  1) as determined by an FDA-approved test, and with disease progression on or after 2 or more prior lines of therapy including fluoropyrimidine- and platinum-based chemotherapy and HER2/neu-targeted therapy (if appropriate); **AND**
13. The patient has not received treatment with another PD-1 inhibitor.

Nivolumab (Opdivo) may be medically necessary when the following criteria are met:

1. The patient has unresectable or metastatic melanoma; **AND**
  - a. Nivolumab is used as monotherapy for patients with BRAF wild-type or mutation-positive disease; **OR**
  - b. Nivolumab is used in combination with ipilimumab, regardless of BRAF status; **OR**
2. The patient has melanoma with lymph node involvement or metastatic disease (Stage IIIB/C or Stage IV); **AND**
  - a. The patient has undergone complete resection; **AND**
  - b. Nivolumab is used as adjuvant treatment; **OR**
3. The patient has advanced metastatic non-small cell lung cancer (NSCLC); **AND**

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- a. For the patient who has EGFR-mutation-positive or ALK-fusion oncogene-positive tumor, there is documentation of disease progression while on FDA-approved therapy for these mutations prior to receiving nivolumab (note: this does not apply if the patient's tumor does not have these mutations); **AND**
- b. The patient has disease progression on or after platinum-based chemotherapy; **OR**
4. The patient has small cell lung cancer with relapse 6 months or less after primary therapy and is receiving nivolumab as subsequent systemic therapy, alone or in combination with ipilimumab (NCCN 2A); **OR**
5. The patient has advanced renal cell carcinoma and has received prior anti-angiogenic therapy; **OR**
6. The patient has intermediate or poor risk, previously untreated advanced renal cell carcinoma and is receiving nivolumab in combination with ipilimumab; **OR**
7. The patient has been diagnosed with classical Hodgkin lymphoma; **AND**
  - a. The patient has relapse or disease progression after autologous hematopoietic stem cell transplantation (HSCT) and post-transplant treatment with brentuximab vedotin; **OR**
  - b. The patient has relapse or disease progression after 3 or more lines of systemic therapy (including autologous HSCT); **AND**
  - c. Nivolumab is used as monotherapy; **OR**
8. The patient has recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after a platinum-based therapy; **OR**
9. The patient has hepatocellular carcinoma and has been previously treated with sorafenib; **OR**
10. The patient has metastatic colorectal cancer with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) biomarkers that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, and the patient will be using nivolumab alone or in combination with ipilimumab; **OR**
11. The patient has locally advanced or metastatic urothelial carcinoma; **AND**
  - a. The patient has disease progression during or following platinum-containing chemotherapy; **OR**
  - b. The patient has disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy; **AND**
12. The patient has not received treatment with another PD-1 inhibitor.

Use of a PD-1 Inhibitor may be considered medically necessary for clinical indications not listed above when the drug is prescribed for the treatment of cancer either:

- In accordance with FDA label (when clinical benefit has been established, see Policy Guidelines); **OR**
- In accordance with specific strong endorsement or support by nationally recognized compendia, when such recommendation is based on strong/high levels of evidence, and/or

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uniform consensus of clinical appropriateness has been reached.

## When PD-1 Inhibitors are not covered

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Pembrolizumab (Keytruda) is considered not medically necessary when criteria under “When PD-1 Inhibitors are covered” are not met.

Nivolumab (Opdivo) is considered not medically necessary when criteria under “When PD-1 Inhibitors are covered” are not met.

PD-1 inhibitors are considered investigational when used for indications outside of FDA labeling and nationally recognized compendia recommendations with the highest level of evidence (i.e. Level 1, 2A, 2B).

PD-1 inhibitors are considered investigational when used for:

1. Non-cancer indications; **OR**
2. When criteria are not met regarding FDA labeling **OR** strong endorsement/support by nationally recognized compendia, as stated under “When PD-1 Inhibitors are covered.”

## Policy Guidelines

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Drugs prescribed for treatment of cancer in accordance with FDA label may be considered medically necessary when clinical benefit has been established, and should not be determined to be investigational as defined in Corporate Medical Policy (CMP), “Investigational (Experimental) Services.”

Please refer to CMP “Investigational (Experimental) Services” for a summary of evidence standards from nationally recognized compendia.

## Billing/Coding/Physician Documentation Information

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This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at [www.bcbsnc.com](http://www.bcbsnc.com). They are listed in the Category Search on the Medical Policy search page.

*Applicable codes: J9271, J9299*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

## Scientific Background and Reference Sources

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Specialty Matched Consultant Advisory Panel 8/2018

### **Policy Implementation/Update Information**

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#### **For Policy Titled: Pembrolizumab (Keytruda)**

- 9/30/14 New medical policy issued. Pembrolizumab (Keytruda) may be medically necessary when the following criteria are met: 1. The patient has unresectable or metastatic melanoma, and disease has progressed following treatment with ipilimumab, and 2. If BRAF V600 mutation positive, disease has progressed following a BRAF inhibitor. Medical director review 9/2014. (sk)
- 12/30/14 Added HCPCS code C9027 to the Billing/Coding section for effective date 1/1/2015. (lpr)

#### **For Policy Re-titled: “Treatments for Metastatic Melanoma”**

- 2/10/15 Policy title changed from “Pembrolizumab (Keytruda)” to “Treatments for Metastatic Melanoma.” Added Nivolumab (Opdivo) as a treatment in the “When Covered” section: Nivolumab (Opdivo) may be medically necessary when the following criteria are met: 1. The patient has unresectable or metastatic melanoma, and disease has progressed following treatment with ipilimumab, and 2. If BRAF V600 mutation positive, disease has progressed following a BRAF inhibitor. Added HCPCS codes C9399, J3490, J9999 to the “Billing/Coding” section. (lpr)
- 4/28/15 Under Policy Guidelines section, added this policy only addresses treatment for Melanoma. (lpr)
- 7/28/15 Added HCPCS codes C9453 and J3590 and deleted HCPCS code C9399 in “Billing/Coding” section for effective date 7/1/15. (lpr)

#### **For Policy Re-titled “PD-1 Inhibitors”**

- 9/1/15 Policy title revised from “Treatments for Metastatic Melanoma” to “PD-1 Inhibitors”. Under “When Covered” section added coverage criteria for NSCLC in statement 3. “The patient has advanced metastatic squamous non-small cell lung cancer (NSCLC) with progression on or after platinum based chemotherapy.” Updated Description and Policy Guidelines sections. Senior Medical Director review 8/2015. References added. Specialty Matched Consultant Advisory Panel review 8/26/2015. (lpr)
- 10/30/15 Revised and updated “When Covered” section: Pembrolizumab (Keytruda) may be medically necessary when the following criteria are met: 1. The patient has unresectable or metastatic melanoma; and a. Keytruda is used as monotherapy for initial therapy for untreated disease, or Keytruda is used as monotherapy for disease progression following treatment with ipilimumab; and b. If BRAF V600 mutation positive, disease has progressed following therapy with a BRAF inhibitor with tumor expression of PD-L1, or 2. The patient has metastatic non-small cell lung cancer (NSCLC) with tumor expression of PD-L1 progression on or after platinum-based therapy; and 3. The patient has not received treatment with another PD-L1 inhibitor. Nivolumab (Opdivo) may be medically necessary when the following criteria are met: 1. The patient has unresectable or metastatic melanoma; and a. Nivolumab is used with or without ipilimumab for



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patients who have a BRAF wild-type mutation; or b.If BRAF V600 mutation positive, disease has progressed following therapy with a BRAF inhibitor; or 2. The patient has advanced metastatic non-small cell lung cancer (NSCLC) progression on or after platinum based chemotherapy; and 3. The patient has not received treatment with another PD-L1 inhibitor.

Updated Policy Guidelines and Description sections. References added. Sr. Medical director review. (lpr)

- 11/24/15 Under “When Covered” section added additional criteria for Keytruda under bullet #2 and also for Opdivo under bullet #2: “and the patient with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Keytruda or Opdivo.” Notification given 11/24/15 for effective date 1/26/16. (lpr)
- 1/26/16 Added HCPCS codes J9271, J9299 and deleted HCPCS codes C9027, C9453, J3490, J3590, J9999 in Billing/Coding section for effective date 1/1/2016. (lpr)
- 2/29/16 Under “When Covered” section: expanded coverage for Keytruda regardless of BRAF mutation status; added renal cell carcinoma coverage indication for Opdivo as well as expanded coverage for use of Opdivo in combination with Yervoy(ipilimumab) regardless of BRAF status. Updated Description and Policy Guidelines sections. Medical Director review. References added. (lpr)
- 4/29/16 Re-formatted covered indications under “When Covered” section for both Keytruda and Opdivo. Under “When Not Covered” section added the following statement: “PD-1 inhibitors are considered investigational when used for indications outside of FDA labeling and nationally recognized compendia recommendations with the highest level of evidence (i.e. Level 1, 2A, 2B).” No change to policy intent. Medical Director review 4/2016. (lpr)
- 7/1/16 Added the following covered indication for Classical Hodgkin lymphoma under “When Covered” #5. a-d. “The patient has been diagnosed with Classical Hodgkin lymphoma: **and** a.the patient has disease progression after autologous hematopoietic stem cell transplantation (HSCT): **and** b. the patient has disease progression after post-transplant treatment with brentuximab vedotin: **and** c. Opdivo is used as monotherapy; d.the patient has not received treatment with another PD-1 inhibitor. Medical director review 6/2016. References added. (lpr)
- 12/30/16 Specialty Matched Consultant Advisory Panel review 8/31/2016. Added covered indications for NSCLC under “When Covered” section Keytruda statements #2 and #3: “The patient has metastatic non-small cell lung cancer (NSCLC) with high PD-L1 tumor expression (Tumor Proportion Score or TPS  $\geq$  50%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, and no prior systemic chemotherapy treatment for metastatic NSCLC” and “The patient has metastatic non-small cell lung cancer (NSCLC) with tumor expression of PD-L1 (TPS  $\geq$  1%) as determined by an FDA-approved test.” Added a covered indication for head and neck squamous cell cancer under “When Covered” section Pembrolizumab (Keytruda) statement #4: “The patient has recurrent or metastatic head and neck squamous cell cancer (HNSCC) with disease progression on or after platinum-containing chemotherapy.” Removed the “L” from PD-1 in statement #5 under Keytruda. Added covered indication for head and neck squamous cell cancer under “When Covered” section Nivolumab (Opdivo) statement #5: “The patient has recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after a platinum-based therapy.” Reference added. Medical Director review 12/2016. Notification given 12/30/16 for effective date 4/1/17. (lpr)

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- 2/24/17 Added the following statement to “When Covered” section: “Use of a PD-1 Inhibitor may be considered medically necessary for clinical indications not listed above when the drug is prescribed for the treatment of cancer either: In accordance with FDA label (when clinical benefit has been established, see Policy Guidelines); OR In accordance with specific strong endorsement or support by nationally recognized compendia, when such recommendation is based on strong/high levels of evidence, and/or uniform consensus of clinical appropriateness has been reached”. Under “When Not Covered” section, added the statement “PD-1 inhibitors are considered investigational when used for: 1)Non-cancer indications; **OR** 2) When criteria are not met regarding FDA labeling **OR** strong endorsement/ support by nationally recognized compendia, as stated under “When PD-1 Inhibitors are covered.” Added the following statements under “Policy Guidelines” section: 1)Drugs prescribed for treatment of cancer in accordance with FDA label may be considered medically necessary when clinical benefit has been established, and should not be determined to be investigational as defined in Corporate Medical Policy, Investigational (Experimental) Services.” 2) Please refer to CMP “Investigational (Experimental) Services” for a summary of evidence standards from nationally recognized compendia. Also added covered indication for urothelial carcinoma under When Covered section: The patient has locally advanced or metastatic urothelial carcinoma and have: disease progression during or following platinum-containing chemotherapy; **AND** disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.” Senior Medical Director review 2/2017. Remains on notice. Effective date 4/1/17. (lpr)
- 6/30/17 Under “When Covered” section for Pembrolizumab (Keytruda): Added 2 covered indications: 4)for unresectable or metastatic solid tumors with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) biomarkers who have progressed following prior treatment and have no alternative treatment options; and 5) the patient has colorectal cancer with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) biomarkers that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. Reference added. (lpr)
- 9/29/17 Specialty Matched Consultant Advisory Panel review 8/30/2017. No change to policy statement. Removed dosage guidelines in the Policy Guidelines section. (lpr)
- 3/29/18 Under “When Covered” section for Nivolumab (Opdivo): Added additional covered indication: “2) The patient has melanoma with lymph node involvement or metastatic disease (Stage IIIB/C or Stage IV); **AND** a.The patient has undergone complete resection; **AND** b.Opdivo is used as adjuvant treatment”. Under “Description of Procedure or Service” section: Added “On December 20, 2017, the U.S. Food and Drug Administration granted approval to nivolumab for the adjuvant treatment of patients with melanoma with lymph node involvement or in patients with metastatic disease who have undergone complete resection”. Typographical errors corrected. References added. (krc)
- 4/13/18 Under “When Covered” section for Pembrolizumab (Keytruda): Added additional covered indication: “7) The patient has locally advanced or metastatic urothelial carcinoma; **AND** a. The patient is not eligible for cisplatin-containing chemotherapy; **OR** b. The patient has disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy; **AND**”. Reference added. (krc)
- 4/27/18 Under “When Covered” section for Pembrolizumab (Keytruda): Added additional covered indication: “4) The patient has metastatic nonsquamous non-small cell lung cancer (NSCLC) and is receiving pembrolizumab (Keytruda) as first-line treatment, in combination with pemetrexed and carboplatin; **OR**”. Under “When Covered” section for Nivolumab (Opdivo): Added additional covered indications: “4) The patient has small cell lung cancer with relapse

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6 months or less after primary therapy and is receiving nivolumab (Opdivo) as subsequent systemic therapy, alone or in combination with ipilimumab (NCCN 2A); OR” and “6) The patient has intermediate or poor risk, previously untreated advanced renal cell carcinoma and is receiving nivolumab (Opdivo) in combination with ipilimumab (Yervoy); OR”. References added. (krc)

10/26/18 Under “When Covered” section for Pembrolizumab (Keytruda), added additional covered indications: 9) classical Hodgkin lymphoma (cHL) that is refractory, or has relapsed after 3 or more prior lines of therapy; 10) recurrent or metastatic cervical cancer with disease progression on or after chemotherapy, and with PD-L1 tumor expression (CPS  $\geq$  1) as determined by an FDA-approved test; 11) primary mediastinal large B-cell lymphoma (PMBCL) that is refractory, or has relapsed following 2 or more prior lines of therapy, AND the patient does not require urgent cytoreductive therapy; and 12) recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma with PD-L1 tumor expression (CPS  $\geq$  1) as determined by an FDA-approved test, and with disease progression on or after 2 or more prior lines of therapy including fluoropyrimidine- and platinum-based chemotherapy and HER2/neu-targeted therapy (if appropriate). Under “When Covered” section for Nivolumab (Opdivo), added additional covered indications: 9) hepatocellular carcinoma and has been previously treated with sorafenib; and 10) metastatic colorectal cancer with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) biomarkers that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, and the patient will be using nivolumab alone or in combination with ipilimumab. Additional minor updates made to “When Covered” section for clarity. Description section updated to reflect additional indications for Keytruda and Opdivo. References added. Specialty Matched Consultant Advisory Panel review 8/22/2018. (krc)

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