Opdivo® (nivolumab)
(Intravenous)

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I. Length of Authorization Δ [1,43,47,49,50,52-54,65,68,72,73,79,81,82,89]

Coverage will be provided for 6 months and may be renewed (unless otherwise specified).

- Use in the treatment of Classical Hodgkin Lymphoma in combination with brentuximab vedotin can be authorized up to a maximum of 12 weeks of therapy (4 doses) and may NOT be renewed.
- Neoadjuvant or Perioperative Therapy of MSI-H/dMMR Gastric and Esophagogastric/Gastroesophageal Junction Cancer can be authorized for a maximum of 12 weeks of pre-operative therapy (6 doses), followed by a maximum of 36 weeks (9 doses) of postoperative therapy after surgery.
- Neoadjuvant treatment of Merkel Cell Carcinoma can be authorized up to a maximum of two (2) doses and may NOT be renewed.
- Neoadjuvant treatment of NSCLC in combination with platinum-doublet chemotherapy may be authorized for a maximum of three (3) doses and may NOT be renewed.
- Neoadjuvant treatment of Cutaneous Melanoma in combination with ipilimumab may be authorized for a maximum of three (3) doses and may NOT be renewed.
- Adjuvant treatment of Cutaneous Melanoma in combination with ipilimumab may be authorized for a maximum of four (4) doses and may NOT be renewed.
- Adjuvant treatment of the following indications may be renewed up to a maximum of one (1) year of therapy*:
  - Cutaneous Melanoma (single agent)
  - Esophageal and Esophagogastric/Gastroesophageal Junction Cancer
  - Urothelial Carcinoma
- The following indications may be renewed up to a maximum of two (2) years of therapy*:
  - Biliary Tract Cancer

- Bone Cancer
- Cervical Cancer
- Esophageal and Esophagogastric/Gastroesophageal Junction Cancer (first-line therapy)
- Gastric Cancer (in combination with fluoropyrimidine- and platinum-containing chemotherapy)
- Kaposi Sarcoma
- Renal Cell Carcinoma (in combination with cabozantinib)
- Malignant Pleural Mesothelioma (initial therapy in combination with ipilimumab)
- Malignant Peritoneal Mesothelioma (initial therapy in combination with ipilimumab)
- Non-Small Cell Lung Cancer (in combination with ipilimumab with or without platinum-doublet chemotherapy)
- Urothelial Carcinoma (first line therapy in combination with gemcitabine and cisplatin, followed by single-agent maintenance therapy)

Note: The maximum number of doses is dependent on the dosing frequency and duration of therapy. Refer to Section V for exact dosage.		
Dosing Frequency	**Maximum length of therapy**	**Maximum number of doses**
2 weeks	1 year	26 doses
	2 years	52 doses
3 weeks	2 years	35 doses
4 weeks	1 year	13 doses
	2 years	26 doses

II. Dosing Limits

A. Quantity Limit (max daily dose) [NDC Unit]:

- Opdivo 40 mg/4 mL single-dose vial: 2 vials per 14 days
- Opdivo 100 mg/10 mL single-dose vial: 3 vials per 14 days
- Opdivo 120 mg/12 mL single-dose vial: 3 vials per 14 days
- Opdivo 240 mg/24 mL single-dose vial: 4 vials per 14 days

B. Max Units (per dose and over time) [HCPCS Unit]:

Indication	Billable Units (BU)	Per unit time (days)
CNS Cancer, HCC, Cutaneous Melanoma, Uveal Melanoma, & MCC	120 BU	21 days
Biliary Tract Cancer (Gallbladder Cancer or Intra-/Extra-Hepatic Cholangiocarcinoma), Bladder/Urothelial Cancer, Bone Cancer, CRC, Appendiceal Adenocarcinoma, Esophageal Cancer, GEJ Cancer, Gastric, SCCHN, HCC, cHL, Kaposi Sarcoma, RCC, MPM, MPeM, Cutaneous Melanoma, MCC, NSCLC, STS, & Cervical Cancer	240 BU	14 days

CNS Cancer, CRC, Esophageal Cancer, MPM, MPeM, Uveal Melanoma, MCC, & Cutaneous Melanoma	340 BU	14 days
CRC, cHL, & RCC	340 BU	21 days
Esophageal Cancer, GEJ Cancer, Gastric Cancer, MPM, MPeM, & NSCLC	360 BU	21 days
Bladder/Urothelial Cancer, Bone Cancer, CRC, Esophageal Cancer, GEJ Cancer, SCCHN, HCC, cHL, RCC, Cutaneous Melanoma, NSCLC, & STS	480 BU	28 days
Uveal Melanoma	1140 BU	14 days

III. Initial Approval Criteria [1]

Coverage is provided for the following conditions:

- Patient is at least 18 years of age (unless otherwise specified); **AND**

Universal Criteria

- Patient has not received previous therapy with a programmed death (PD-1/PD-L1)-directed therapy (e.g., cemiplimab, avelumab, pembrolizumab, atezolizumab, durvalumab, dostarlimab, nivolumab/relatlimab-rmbw, retifanlimab, toripalimab, etc.), unless otherwise specified ᐞ; **AND**

Biliary Tract Cancers (Gallbladder Cancer or Intra-/Extra-Hepatic Cholangiocarcinoma) ‡ [2,72,177e]

- Patient has tumor mutational burden-high (TMB-H) [≥ 10 mutations/megabase (mut/Mb)] disease as determined by an FDA-approved or CLIA-compliant test❖; **AND**
- Used as subsequent treatment for progression on or after systemic treatment for unresectable, resected gross residual (R2), or metastatic disease; **AND**
- Used in combination with ipilimumab; **AND**
- Disease is refractory to standard therapies or there are no standard treatment options available; **AND**

• Use of nivolumab will be restricted to patients with a contraindication or intolerance to pembrolizumab

Urothelial Carcinoma (Bladder Cancer) † ‡ [1,2,30,51,62,92]

- Used as a single agent; **AND**
  - Used for disease that progressed during or following platinum-containing chemotherapy*; **AND**
    - Patient has one of the following diagnoses:
      - Locally advanced or metastatic urothelial carcinoma †
      - Muscle invasive bladder cancer with local recurrence or persistent disease in a preserved bladder

- Metastatic or local bladder cancer recurrence post-cystectomy
- Recurrent or metastatic primary carcinoma of the urethra; **AND**
  - Patient does not have recurrence of stage T3-4 disease or palpable inguinal lymph nodes
- Metastatic upper genitourinary (GU) tract tumors ‡; **OR**

  - Used as adjuvant therapy †; **AND**
    - Patient has urothelial carcinoma of the bladder, ureter, or renal pelvis; **AND**
    - Patient underwent radical surgical resection; **AND**
    - Patient is at high risk for disease recurrence**; **OR**

- Used in combination with cisplatin and gemcitabine followed by nivolumab maintenance therapy; **AND**
  - Used as first-line systemic therapy in cisplatin eligible patients*; **AND**
    - Patient has one of the following diagnoses:
      - Locally advanced, unresectable, or metastatic urothelial carcinoma †
      - Muscle invasive bladder cancer with local recurrence or persistent disease in a preserved bladder
      - Metastatic or local bladder cancer recurrence post-cystectomy
      - Recurrent or metastatic primary carcinoma of the urethra; **AND**
        - Patient does not have recurrence of stage T3-4 disease or palpable inguinal lymph nodes
      - Metastatic upper genitourinary (GU) tract tumors

Note: [10,51,60,70]

– *If patient was progression free for >12 months after platinum therapy, consider re-treatment with platinum-based therapy if the patient is still platinum eligible (see below for cisplatin- or platinum-ineligible comorbidities).*

- *Cisplatin-ineligible comorbidities may include the following: CrCl < 60 mL/min, ECOG PS ≥ 2 or KPS ≤ 70%, hearing loss of ≥ 25 decibels (dB) at two contiguous frequencies, grade ≥ 2 peripheral neuropathy, or NYHA Heart Failure class ≥ 3. Carboplatin may be substituted for cisplatin in the metastatic setting for cisplatin-ineligible patients such as those with a GFR less than 60 mL/min.*
- *Platinum-ineligible comorbidities may include the following: CrCl < 30 mL/min, ECOG PS ≥ 3, grade ≥ 2 peripheral neuropathy, or NYHA Heart Failure class > 3, etc.*

****Note:*** [1,62]

– *High risk for disease recurrence is defined as:*

- *ypT2-ypT4a or ypN+ for patients who received neoadjuvant cisplatin (excluding prostate with stromal invasion); **OR***
- *pT3-pT4a or pN+ for patients who did not receive neoadjuvant cisplatin and are also ineligible for or refused adjuvant cisplatin therapy (excluding ureter or renal pelvis)*

Bone Cancers ‡ [2,72,177e]

- Patient has one of the following: Ewing Sarcoma, Chondrosarcoma *(excluding mesenchymal chondrosarcoma)*, Osteosarcoma, or Chordoma; **AND**
- Patient has tumor mutation burden-high (TMB-H) [≥ 10 mutations/megabase (mut/Mb)] disease as determined by an FDA-approved or CLIA-compliant test❖; **AND**
- Used in combination with ipilimumab; **AND**
- Patient has unresectable or metastatic disease that progressed following prior treatment; **AND**
- Patient has no satisfactory alternative treatment options; **AND**

• Use of nivolumab will be restricted to patients with a contraindication or intolerance to pembrolizumab

Adult Central Nervous System (CNS) Cancers ‡ [2,5,34,41,42]

- Used in one of the following treatment settings:
  - Used as initial treatment in patients with small asymptomatic brain metastases
  - Used for relapsed limited brain metastases with either stable systemic disease or reasonable systemic treatment options
  - Patient has recurrent limited brain metastases
  - Used for recurrent extensive brain metastases with stable systemic disease or reasonable systemic treatment options; **AND**
- Used in combination with ipilimumab for the treatment of brain metastases in patients with BRAF non-specific melanoma

Cervical Cancer ‡ [2,49,63]

- Used as subsequent therapy as a single agent; **AND**
- Patient has recurrent or metastatic disease; **AND**
- Tumor expresses PD-L1 (e.g., CPS ≥1) as determined by an FDA-approved or CLIA-compliant test❖

Colorectal Cancer (CRC) † ‡ [1,2,31,32,59,106e,107e]

- Patient is at least 12 years of age; **AND**
- Patient has microsatellite instability-high (MSI-H)/mismatch repair deficient (dMMR) disease OR polymerase epsilon/delta (POLE/POLD1) mutation as determined by an FDA-approved or CLIA-compliant test❖; **AND**
  - Used as subsequent therapy; **AND**
    - Used as a single agent or in combination with ipilimumab*; **AND**
    - Patient has metastatic, unresectable, or medically inoperable disease; **AND**

        - Disease progressed following treatment with a fluoropyrimidine-, oxaliplatin-, and/or irinotecan-based chemotherapy; **OR**
    - Used as primary or initial treatment; **AND**
        - Used in combination with ipilimumab; **AND**
            - Used for isolated pelvic/anastomotic recurrence of rectal cancer; **OR**
            - Patient has T3, N Any; T1-2, N1-2; T4, N Any rectal cancer; **OR**
            - Patient has metastatic, unresectable, or medically inoperable disease

***** *Single agent nivolumab should be used in patients who are not candidates for intensive therapy*

Esophageal Cancer and Esophagogastric/Gastroesophageal Junction Cancers † ‡ Φ
1,2,44,52,56,69,133e,158e

- Used as first-line therapy; **AND**
    - Patient has esophageal squamous cell carcinoma †; **AND**
        - Patient is not a surgical candidate or has unresectable advanced, recurrent, or metastatic disease; **AND**
            - Used in combination with ipilimumab; **AND**

> ➢ Use of nivolumab will be restricted to patients with a contraindication or intolerance to one of the following:
>
> ♦ Nivolumab/(fluorouracil or capecitabine)/(cisplatin or oxaliplatin)
>
> ♦ Pembrolizumab/(fluorouracil or capecitabine)/(cisplatin or oxaliplatin) *(CPS ≥10 only)*; **OR**

            - Used in combination with fluorouracil or capecitabine AND cisplatin or oxaliplatin; **OR**
    - Patient has adenocarcinoma; **AND**
        - Patient is not a surgical candidate or has unresectable advanced, recurrent, or metastatic disease; **AND**
        - Used in combination with oxaliplatin and either fluorouracil or capecitabine for HER2 negative disease*; **AND**
        - Patient has a Combined Positive Score (CPS) ≥5 as determined by an FDA-approved or CLIA-compliant test❖; **OR**
- Used as subsequent therapy; **AND**
    - Patient has esophageal squamous cell carcinoma †; **AND**
    - Patient is not a surgical candidate or has unresectable advanced, recurrent, or metastatic disease; **AND**
    - Used as a single agent; **AND**
    - Patient is refractory or intolerant to at least one prior fluoropyrimidine- and platinum-based regimen; **OR**
- Used as adjuvant treatment of completely resected disease †; **AND**

- Used as a single agent in patients with residual disease following neoadjuvant chemoradiotherapy (CRT); **OR**

- Used as neoadjuvant or perioperative therapy; **AND**
  - Patient has microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) disease as determined by an FDA-approved or CLIA-compliant test❖; **AND**
  - Patient has esophagogastric/gastroesophageal junction adenocarcinoma; **AND**
    - Used in combination with ipilimumab; **AND**
      - Used as primary treatment for patients who are medically fit for surgery with cT2, N0 (high-risk lesions: lymphovascular invasion, ≥ 3cm, poorly differentiated), cT1b-cT2, N+ or cT3-cT4a, Any N disease; **OR**
    - Used as a single agent; **AND**
      - Used as postoperative management following R0 resection in patients who have received preoperative therapy with nivolumab and ipilimumab

Note: Combination therapy with oxaliplatin and fluorouracil or capecitabine may also be used for patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) disease as determined by an FDA-approved or CLIA-compliant test❖

Gastric Cancer † ‡ Φ [1,2,53,56]

- Used as first-line therapy; **AND**
  - Patient is not a surgical candidate or has unresectable, advanced, recurrent, or metastatic disease; **AND**
  - Used in combination with oxaliplatin and either fluorouracil or capecitabine for HER2 negative disease*; **AND**
  - Patient has a Combined Positive Score (CPS) ≥5 as determined by an FDA-approved or CLIA-compliant test❖; **OR**
- Used as neoadjuvant or perioperative therapy; **AND**
  - Patient has microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) disease as determined by an FDA-approved or CLIA-compliant test❖; **AND**
    - Used in combination with ipilimumab; **AND**
      - Used as primary treatment prior to surgery for potentially resectable locoregional disease (cT2 or higher, any N) in patients who are medically fit for surgery; **OR**
    - Used as a single agent; **AND**
      - Used as postoperative management following R0 resection in patients who have received preoperative therapy with nivolumab and ipilimumab

Note: Combination therapy with oxaliplatin and fluorouracil or capecitabine may also be used for patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) disease as determined by an FDA-approved or CLIA-compliant test❖

Squamous Cell Carcinoma of the Head and Neck (SCCHN) † ‡ [1,2,29,78]

- Patient has Very Advanced Head and Neck Cancer*; **AND**
- Patient has NON-nasopharyngeal cancer; **AND**
  - Used as a single agent; **AND**
    - Patient has unresectable, recurrent, persistent, or metastatic disease; **AND**
    - Disease has progressed on or after platinum-containing chemotherapy; **AND**
    - Patient has PD-L1 expression ≥1% as determined by an FDA-approved or CLIA-compliant test❖; **OR**
  - Used in combination with cetuximab for patients with performance status (PS) 0-1; **AND**
    - Used as first-line therapy; **AND**
    - Used for one of the following:
      - Metastatic disease at initial presentation
      - Recurrent/persistent disease with distant metastases
      - Unresectable locoregional recurrence with prior RT
      - Unresectable second primary with prior RT
      - Unresectable persistent disease with prior RT; **AND**

▪ Use of nivolumab will be restricted to patients with a contraindication or intolerance to one of the following: – Pembrolizumab monotherapy *(patients with CPS ≥1)* – Generically available agent/regimen (e.g., cisplatin/paclitaxel, etc. *[see NCCN Head and Neck Cancers guideline for complete list of alternatives]*)

** Very Advanced Head and Neck Cancer includes: newly diagnosed locally advanced T4b (M0) disease, newly diagnosed unresectable regional nodal disease (typically N3), metastatic disease at initial presentation (M1), or recurrent or persistent disease.*

Hepatocellular Carcinoma (HCC) † ‡ Φ [1,2,21,86,87,38e-40e]

- Used for one of the following:
  - Patient was previously treated with sorafenib †
  - Patient has unresectable disease and is not a transplant candidate
  - Patient has liver-confined disease that is inoperable by performance status, comorbidity, or with minimal or uncertain extrahepatic-disease
  - Patient has metastatic disease or extensive liver tumor burden; **AND**
- Used in combination with ipilimumab; **AND**
  - Patient has Child-Pugh Class A hepatic impairment; **AND**
  - Used as subsequent therapy for progressive disease; **AND**

<u>Patients with AFP ≥ 400 ng/mL ONLY:</u>

- Use of nivolumab in combination with ipilimumab will be restricted to patients with a contraindication or intolerance to ramucirumab

Adult Classical Hodgkin Lymphoma (cHL) † ‡ Φ [1,2,27,28,73,54,75e]

- Used as a single agent; **AND**
  - Patient has relapsed or progressive disease after autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin †; **OR**
  - Used for disease that is refractory to at least 3 prior lines of therapy including autologous HSCT †; **OR**
- Used in combination with brentuximab vedotin in patients 18 to 60 years of age; **AND**
  - Used as second-line therapy for relapsed or refractory disease; **OR**
  - Used as subsequent therapy (if not previously used) for relapsed or refractory disease; **AND**
    - Patient has a Deauville scale score of 4 or 5 following restaging with FDG-PET/CT

Pediatric Classical Hodgkin Lymphoma (cHL) ‡ [2,27,28,55]

- Patient is ≤ 18 years of age*; **AND**
- Patient has relapsed or refractory disease; **AND**
- Used in patients heavily pretreated with platinum or anthracycline-based chemotherapy or if a decrease in cardiac function was observed; **AND**
- Used as subsequent therapy (if not previously used); **AND**
- Used in combination with brentuximab vedotin

** Pediatric Hodgkin Lymphoma may be applicable to adolescent and young adult (AYA) patients up to the age of 39 years.*

Kaposi Sarcoma ‡ [2,79]

- Used in combination with ipilimumab as subsequent therapy; **AND**
- Patient has classic disease; **AND**
- Used for relapsed/refractory advanced cutaneous, oral, visceral, or nodal disease; **AND**
- Disease has progressed on or not responded to first-line therapy; **AND**
- Disease has progressed on alternate first-line therapy

Renal Cell Carcinoma (RCC) † ‡ [1,2,25,26,66e,164e]

- Used in combination with ipilimumab; **AND**
  - Patient has clear cell histology; **AND**
    - Used as first-line therapy in patients with poor or intermediate risk advanced, relapsed, or stage IV disease; **OR**

        - Used as first-line therapy in patients with favorable risk relapsed or stage IV disease; **OR**
- Used as a single agent; **AND**
    - Used as subsequent therapy in patients with advanced, relapsed, or stage IV disease and clear cell histology; **OR**
- Used in combination with cabozantinib (Cabometyx only); **AND**
    - Patient has clear cell histology; **AND**
        - Used as first-line therapy for advanced, relapsed, or stage IV disease; **AND**
        - Use of nivolumab will be restricted to patients with a contraindication or intolerance to pembrolizumab/(axitinib or lenvatinib); **OR**
    - Patient has non-clear cell histology; **AND**
        - Patient has relapsed or stage IV disease; **AND**
        - Patient does not have chromophobe RCC

Cutaneous Melanoma † ‡ Φ [1,2,15-18,82,93,14e,150e-152e]

- Used as first-line therapy for unresectable or metastatic* disease; **AND**
    - Patient is at least 12 years of age; **AND**
    - Used as a single agent or in combination with ipilimumab; **OR**
- Used as subsequent therapy for unresectable or metastatic* disease; **AND**
    - Patient is at least 12 years of age; **AND**
        - Used after disease progression, intolerance, and/or projected risk of progression with BRAF-targeted therapy (e.g., dabrafenib/trametinib, vemurafenib/cobimetinib, encorafenib/binimetinib, etc.); **AND**
            - Used as a single agent or in combination with ipilimumab if anti-PD-1 therapy was not previously used; **OR**
            - Used in combination with ipilimumab for disease progression on single agent anti-PD-1 therapy; **OR**
- Used as adjuvant treatment; **AND**
    - Used as a single agent; **AND**
        - Patient is at least 12 years of age; **AND**
            - Patient has stage IIB, IIC, IIIB, IIIC, or metastatic disease †; **AND**
                - Patient has undergone complete resection †; **OR**
            - Patient has oligometastatic disease and no evidence of disease (NED) following metastasis-directed therapy (i.e., stereotactic ablative therapy or complete resection) or systemic therapy followed by resection; **OR**
    - Used in combination with ipilimumab; **AND**

        - Patient has oligometastatic disease and no evidence of disease (NED) following metastasis-directed therapy (i.e., complete resection, stereotactic ablative therapy or T-VEC/intralesional therapy) or systemic therapy followed by resection
- Used as neoadjuvant therapy; **AND**
    - Used in combination with ipilimumab; **AND**
        - Patient has stage III disease; **AND**
            - Used as primary treatment for clinically positive, resectable nodal disease; **OR**
        - Patient has resectable disease limited to nodal recurrence

**Metastatic disease includes stage III unresectable/borderline resectable disease with clinically positive node(s) or clinical satellite/in-transit metastases, or as well as unresectable local satellite/in-transit recurrence, unresectable nodal recurrence, and widely disseminated distant metastatic disease.*

Uveal Melanoma ‡ [2,19,20,80]

- Patient has metastatic or unresectable disease; **AND**
- Used as first-line therapy in combination with ipilimumab

Merkel Cell Carcinoma ‡ [2,4,33,65]

- Used as neoadjuvant treatment; **AND**
    - Used as a single agent; **AND**
        - Patient is a surgical candidate with primary clinical N0 locally advanced disease where curative surgery and curative radiation therapy were originally deemed not feasible; **OR**
        - Patient has primary clinical N+, M0 regional disease with biopsy positive draining nodal basin; **OR**
- Used for M1 disseminated disease; **AND**
    - Used as a single agent; **OR**
    - Used in combination with ipilimumab; **AND**
        - Patient progressed on anti-PD-L1 or anti-PD-1 therapy OR anti-PD-L1 or anti-PD-1 therapy is contraindicated

Malignant Peritoneal Mesothelioma (MPeM) ‡ [2,64,90]

- Used as a single agent as subsequent therapy (if platinum chemotherapy was administered first-line)

Malignant Pleural Mesothelioma (MPM) † ‡ Φ [1,2,37,38,47,64,81]

- Used as a single agent or in combination with ipilimumab as subsequent therapy (if platinum chemotherapy was administered first-line); **OR**
- Used in combination with ipilimumab as first-line therapy; **AND**
    - Disease is medically inoperable or unresectable

Non-Small Cell Lung Cancer (NSCLC) † ‡ [1,2,11,22,23,43,45,46,43e-45e,51e-53e,56e,125e,127e,166e,191e-193e]

- Used as neoadjuvant therapy for resectable (tumors ≥ 4 cm or node positive) disease; **AND**
  - Used in combination with platinum-doublet chemotherapy (e.g., cisplatin/carboplatin in combination with paclitaxel, pemetrexed, or gemcitabine); **AND**
  - Patient is negative for EGFR or ALK rearrangements; **OR**
- Used for recurrent, advanced, or metastatic disease (excluding locoregional recurrence or symptomatic local disease without evidence of disseminated disease) or mediastinal lymph node recurrence with prior radiation therapy; **AND**
  - Used as first-line therapy; **AND**
    - Used for one of the following:
      - Patients with a performance status (PS) 0-1 who have tumors that are negative for actionable molecular biomarkers**** ¥** and PD-L1 expression <1%
      - Patients with a PS 0-1 who are positive for one of the following molecular biomarkers: EGFR exon 20, KRAS G12C, BRAF V600E, NTRK1/2/3 gene fusions, MET exon 14 skipping, RET rearrangement, or ERBB2 (HER2)
      - PD-L1 expression-positive (PD-L1 ≥1%) tumors, as detected by an FDA or CLIA compliant test❖, that are negative for actionable molecular biomarkers** ¥; AND
    - Used in combination with one of the following:
      - Ipilimumab
      - Ipilimumab and platinum-doublet chemotherapy (e.g., pemetrexed and either carboplatin or cisplatin for nonsquamous cell histology, or paclitaxel and carboplatin for squamous cell histology, etc.); **AND**

Squamous NSCLC:

- Use of nivolumab in combination with ipilimumab (with or without platinum-doublet chemotherapy) will be restricted to patients with a contraindication or intolerance to cemiplimab/paclitaxel/(carboplatin or cisplatin); **OR**

Nonsquamous NSCLC:

- Use of nivolumab in combination with ipilimumab (with or without platinum-doublet chemotherapy) will be restricted to patients with a contraindication or intolerance to cemiplimab/(paclitaxel or pemetrexed)/(carboplatin or cisplatin); **OR**

  - Used as subsequent therapy; **AND**
    - Used as a single agent; **OR**
    - Used for one of the following:
      - Patients with a PS 0-1 who are positive for one of the following molecular biomarkers and have received prior targeted therapy**§**: EGFR exon 19

deletion or exon 21 L858R tumors, EGFR S768I, L861Q, and/or G719X, ALK rearrangement, or ROS1 rearrangement

- Patients with a PS 0-1 who are positive for one of the following molecular biomarkers: BRAF V600E, NTRK1/2/3 gene fusions, MET exon 14 skipping, or RET rearrangement; **AND**

➢ Used in combination with one of the following:

- Ipilimumab
- Ipilimumab, pemetrexed, and either carboplatin or cisplatin for nonsquamous cell histology
- Ipilimumab, paclitaxel, and carboplatin for squamous cell histology; **AND**

Squamous NSCLC:

➢ Use of nivolumab in combination with ipilimumab (with or without platinum-doublet chemotherapy) will be restricted to patients with a contraindication or intolerance to cemiplimab/paclitaxel/(carboplatin or cisplatin); **OR**

Nonsquamous NSCLC:

➢ Use of nivolumab in combination with ipilimumab (with or without platinum-doublet chemotherapy) will be restricted to patients with a contraindication or intolerance to cemiplimab/(paclitaxel or pemetrexed)/(carboplatin or cisplatin); **OR**

- Used as continuation maintenance therapy in combination with ipilimumab; **AND**
  - Patient has achieved a response or stable disease following first-line therapy with nivolumab and ipilimumab with or without chemotherapy

******** *Note: Actionable molecular genomic biomarkers include EGFR, KRAS, ALK, ROS1, BRAF, NTRK1/2/3, MET, RET, and ERBB2 (HER2). Complete genotyping for EGFR, KRAS, ALK, ROS1, BRAF, NTRK1/2/3, MET, RET, and ERBB2 (HER2) via biopsy and/or plasma testing. If a clinically actionable marker is found, it is reasonable to start therapy based on the identified marker. Treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes.*

¥ *May also be used for patients with KRAS G12C mutation positive tumors.*

Soft Tissue Sarcoma ‡ [2,72,84]

- Extremity/Body Wall, Head/Neck***** or Retroperitoneal/Intra-Abdominal******
  - Used as a single agent or in combination with ipilimumab; **AND**
  - Used as subsequent therapy; **AND**
  - Patient has tumor mutational burden-high (TMB-H) [≥ 10 mutations/megabase (mut/Mb)] disease as determined by an FDA-approved or CLIA-compliant test❖; **AND**

- Patient has no satisfactory alternative treatment options; **OR**

- Pleomorphic Rhabdomyosarcoma
  - Used as a single agent or in combination with ipilimumab; **AND**
  - Used as subsequent therapy; **AND**
  - Patient has tumor mutational burden-high (TMB-H) [≥ 10 mutations/megabase (mut/Mb)] disease as determined by an FDA-approved or CLIA-compliant test❖; **AND**
  - Patient has no satisfactory alternative treatment options

***For atypical lipomatous tumor/well-differentiated liposarcoma (ALT/WDLS) of the extremity, abdominal wall, trunk that was initially diagnosed as ALT and shows evidence of de-differentiation, treat as other soft tissue sarcomas.*

***For well-differentiated liposarcoma (WDLS-retroperitoneum, paratesticular) with or without evidence of de-differentiation, treat as other soft tissue sarcomas; risk of WDLS progression without de-differentiation is low and therefore single-agent systemic therapy is recommended.*

Preferred therapies and recommendations are determined by review of clinical evidence. NCCN category of recommendation is taken into account as a component of this review. Regimens deemed equally efficacious (i.e., those having the same NCCN categorization) are considered to be therapeutically equivalent.

❖ *If confirmed using an FDA approved assay – http://www.fda.gov/CompanionDiagnostics*

† FDA Approved Indication(s); ‡ Compendia Recommended Indication(s); Φ Orphan Drug

§ Genomic Aberration/Mutational Driver Targeted Therapies (Note: *not all inclusive, refer to guidelines for appropriate use*)			
EGFR exon 19 deletion or exon 21 L858R tumors	*EGFR* S768I, L861Q, and/or G719X mutation positive tumors	*EGFR* exon 20 insertion mutation positive tumors	*NTRK1/2/3* gene fusion positive tumors
– Afatinib – Erlotinib – Dacomitinib – Gefitinib – Osimertinib – Amivantamab	– Afatinib – Erlotinib – Dacomitinib – Gefitinib – Osimertinib	– Amivantamab	– Larotrectinib – Entrectinib
ALK rearrangement-positive tumors	*ROS1* rearrangement-positive tumors	*BRAF* V600E-mutation positive tumors	*ERBB2 (HER2)* mutation positive tumors
– Alectinib – Brigatinib – Ceritinib – Crizotinib – Lorlatinib	– Ceritinib – Crizotinib – Entrectinib – Lorlatinib – Repotrectinib	– Dabrafenib ± trametinib – Encorafenib + binimetinib – Vemurafenib	– Fam-trastuzumab deruxtecan-nxki – Ado-trastuzumab emtansine
PD-L1 tumor expression ≥ 1%	*MET* exon-14 skipping mutations	*RET* rearrangement-positive tumors	*KRAS G12C* mutation positive tumors
– Pembrolizumab – Atezolizumab – Nivolumab + ipilimumab – Cemiplimab – Tremelimumab + durvalumab	– Capmatinib – Crizotinib – Tepotinib	– Selpercatinib – Cabozantinib – Pralsetinib	– Sotorasib – Adagrasib

IV. Renewal Criteria Δ 1,2,4-6,15-42,43,47,49,50,52-54,68,72,73,79,81,82,89

Coverage may be renewed based upon the following criteria:

- Patient continues to meet the universal and other indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified in section III; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: severe infusion-related reactions, complications of allogeneic hematopoietic stem cell transplantation (HSCT), severe immune-mediated adverse reactions (i.e., pneumonitis, colitis, hepatitis/hepatotoxicity, endocrinopathies, nephritis/renal dysfunction, adverse skin reactions/rash, etc.), etc.; **AND**
- Disease response with treatment as defined by stabilization of disease or decrease in size of tumor or tumor spread; **AND**
- For the following indications, patient has not exceeded a maximum of two (2) years of therapy*:
  - Biliary Tract Cancer
  - Bone Cancer
  - Cervical Cancer
  - Esophageal and Esophagogastric/Gastroesophageal Junction Cancer (first-line therapy)
  - Gastric Cancer (in combination with fluoropyrimidine- and platinum-containing chemotherapy)
  - Kaposi Sarcoma
  - Renal Cell Carcinoma (in combination with cabozantinib)
  - Malignant Pleural Mesothelioma (initial therapy in combination with ipilimumab)
  - Malignant Peritoneal Mesothelioma (initial therapy in combination with ipilimumab)
  - Non-Small Cell Lung Cancer (in combination with ipilimumab with or without platinum-doublet chemotherapy)
  - Urothelial Carcinoma (first line therapy in combination with gemcitabine and cisplatin, followed by single-agent maintenance therapy)

Urothelial Carcinoma (adjuvant therapy)*

- Patient has not exceeded a maximum of one (1) year of therapy

Esophageal and Esophagogastric/Gastroesophageal Junction Cancer (adjuvant therapy)*

- Patient has not exceeded a maximum of one (1) year of therapy

MSI-H/dMMR Gastric and Esophagogastric/Gastroesophageal Junction Cancer (neoadjuvant or perioperative therapy)

- Patient has not exceeded a maximum of 12 weeks of pre-operative therapy (6 doses), followed by a maximum of 36 weeks (9 doses) of postoperative therapy after surgery

Classical Hodgkin Lymphoma (in combination with brentuximab vedotin)

- Patient has not exceeded a maximum of 12 weeks of therapy (4 doses)

Cutaneous Melanoma (adjuvant therapy as a single agent)*

- Patient has not exceeded a maximum of one (1) year of therapy

Cutaneous Melanoma (adjuvant therapy in combination with ipilimumab)

- Patient has not exceeded a maximum of four (4) doses

Cutaneous Melanoma (neoadjuvant therapy in combination with ipilimumab)

- Patient has not exceeded a maximum of three (3) doses

Merkel Cell Carcinoma (neoadjuvant therapy)

- Patient has not exceeded a maximum of two (2) doses

Non-Small Cell Lung Cancer (neoadjuvant therapy in combination with platinum-doublet chemotherapy)

- Patient has not exceeded a maximum of three (3) doses

Non-Small Cell Lung Cancer (maintenance therapy)

- *Refer to Section III for criteria*

Δ Notes:

- Patients responding to therapy who relapse ≥ 6 months after discontinuation due to duration (i.e., receipt of 24 months of therapy) are eligible to re-initiate PD-directed therapy.
- Patients previously presenting with aggressive disease who are exhibiting stable disease on treatment as their best response (or if therapy improved performance status) may be eligible for continued therapy beyond the 24-month limit without interruption or discontinuation.
- Patients who complete adjuvant therapy and progress ≥ 6 months after discontinuation are eligible to re-initiate PD-directed therapy for metastatic disease.
- Patients whose tumors, upon re-biopsy, demonstrate a change in actionable mutation (e.g., MSS initial biopsy; MSI-H subsequent biopsy) may be eligible to re-initiate PD-directed therapy and will be evaluated on a case-by-case basis.

V. Dosage/Administration Δ [1,4-6,19,20,27,24,31-42,48-50,52-54,55,58,59,61,65,67,68,71-80-86,87,89,91,93,96]

Indication	Dose

Biliary Tract Cancers	Administer 240 mg intravenously every 2 weeks (given in combination with ipilimumab every 6 weeks) until disease progression or unacceptable toxicity for up to 24 months (2 years)
Urothelial Carcinoma (Bladder Cancer)	First-line therapy: • Administer 360 mg intravenously every 3 weeks for up to 6 cycles (given in combination with gemcitabine and cisplatin), followed by a single-agent maintenance dose of 240 mg intravenously every 2 weeks or 480 mg intravenously every 4 weeks until disease progression or unacceptable toxicity for up to 24 months (2 years) Disease progression or second-line treatment: • Administer 240 mg intravenously every 2 weeks or 480 mg intravenously every 4 weeks until disease progression or unacceptable toxicity Adjuvant treatment: • Administer 240 mg intravenously every 2 weeks or 480 mg intravenously every 4 weeks until disease recurrence or unacceptable toxicity for up to 1 year
Bone Cancer	Administer 240 mg intravenously every 2 weeks (given in combination with ipilimumab every 6 weeks) until disease progression or unacceptable toxicity for up to 24 months (2 years)
Adult CNS Cancers	**Metastases from Melanoma** Single agent: • Administer 3 mg/kg intravenously every 2 weeks until disease progression or unacceptable toxicity In combination with ipilimumab: • Administer 1 mg/kg intravenously every 3 weeks for 4 doses (given in combination with ipilimumab on the same day), then 3 mg/kg intravenously every 2 weeks until disease progression or unacceptable toxicity
Colorectal Cancer (CRC)	Adult patients and for pediatric patients ≥ 12 years and ≥ 40 kg: • **Single agent:** Administer 3 mg/kg intravenously every 2 weeks, or 240 mg intravenously every 2 weeks, or 480 mg intravenously every 4 weeks until disease progression or unacceptable toxicity • **In combination with ipilimumab:** Primary/initial treatment ○ Administer 3 mg/kg intravenously every 2 weeks (given in combination with ipilimumab every 6 weeks) until disease progression or unacceptable toxicity Subsequent therapy ○ Administer 3 mg/kg intravenously every 3 weeks for 4 doses (given in combination with ipilimumab on the same day), then follow with the single agent regimen Pediatric patients ≥ 12 years and < 40 kg: • **Single agent:** Administer 3 mg/kg intravenously every 2 weeks until disease progression or unacceptable toxicity • **In combination with ipilimumab:**

	Primary/initial treatment ○ Administer 3 mg/kg intravenously every 2 weeks (given in combination with ipilimumab every 6 weeks) until disease progression or unacceptable toxicity Subsequent therapy ○ Administer 3 mg/kg intravenously every 3 weeks for 4 doses (given in combination with ipilimumab on the same day), then follow with the single agent regimen
Esophageal Cancer **(Squamous Cell Carcinoma)**	First-line therapy: • Administer 240 mg intravenously every 2 weeks or 360 mg intravenously every 3 weeks or 480 mg intravenously every 4 weeks (given in combination with fluoropyrimidine- and platinum-containing chemotherapy) until disease progression or unacceptable toxicity for up to 2 years • Administer 3 mg/kg intravenously every 2 weeks or 360 mg intravenously every 3 weeks (given in combination with ipilimumab every 6 weeks) until disease progression or unacceptable toxicity for up to 2 years Subsequent therapy: • Administer 240 mg intravenously every 2 weeks or 480 mg intravenously every 4 weeks until disease progression or unacceptable toxicity
Esophageal and Esophagogastric/ Gastroesophageal Junction Cancer **(Adjuvant Therapy)**	Administer 240 mg intravenously every 2 weeks or 480 mg intravenously every 4 weeks for up to 1 year
MSI-H/dMMR Gastric and Esophagogastric/ Gastroesophageal Junction Cancer	Neoadjuvant/perioperative therapy (adenocarcinoma only): • Administer 240 mg intravenously every 2 weeks (given in combination with ipilimumab every 6 weeks) for 12 weeks, followed by surgery and then post-operative therapy *(See below)* Post-operative therapy (adenocarcinoma only): • Administer 480 mg intravenously every 4 weeks for 36 weeks (9 cycles)
Esophageal and Esophagogastric/ Gastroesophageal Junction Cancer **(Adenocarcinoma)**	First-line therapy: Administer 240 mg intravenously every 2 weeks or 360 mg intravenously every 3 weeks (given in combination with fluoropyrimidine- and platinum-containing chemotherapy) until disease progression or unacceptable toxicity for up to 2 years
Gastric Cancer	Administer 240 mg intravenously every 2 weeks or 360 mg intravenously every 3 weeks until disease progression or unacceptable toxicity for up to 2 years
SCCHN	Single agent: • Administer 240 mg intravenously every 2 weeks or 480 mg intravenously every 4 weeks until disease progression or unacceptable toxicity In combination with cetuximab: • Administer 240 mg intravenously every 2 weeks until disease progression or unacceptable toxicity

Hepatocellular Carcinoma (HCC)	Single agent: • Administer 240 mg intravenously every 2 weeks or 480 mg intravenously every 4 weeks until disease progression or unacceptable toxicity In combination with ipilimumab: • Administer 1 mg/kg intravenously every 3 weeks for 4 doses (given in combination with ipilimumab on the same day), then 240 mg intravenously every 2 weeks or 480 mg intravenously every 4 weeks until disease progression or unacceptable toxicity
Adult cHL	Single agent: • Administer 240 mg intravenously every 2 weeks or 480 mg intravenously every 4 weeks until disease progression or unacceptable toxicity In combination with brentuximab vedotin • Administer 3 mg/kg intravenously every 3 weeks for up to 12 weeks (4 cycles)
Pediatric cHL	In combination with brentuximab vedotin • Administer 3 mg/kg intravenously every 3 weeks for up to 12 weeks (4 cycles)
Kaposi Sarcoma	Administer 240 mg intravenously every 2 weeks (given in combination with ipilimumab every 6 weeks) until disease progression or unacceptable toxicity for up to 24 months (2 years)
Renal Cell Carcinoma (RCC)	Single agent: • Administer 240 mg intravenously every 2 weeks or 480 mg intravenously every 4 weeks until disease progression or unacceptable toxicity In combination with ipilimumab: • Administer 3 mg/kg intravenously every 3 weeks for 4 doses (given in combination with ipilimumab on the same day), then follow with the single agent regimen until disease progression or unacceptable toxicity In combination with cabozantinib (Cabometyx): • Administer 240 mg intravenously every 2 weeks or 480 mg intravenously every 4 weeks until disease progression or unacceptable toxicity for up to 2 years
Malignant Peritoneal Mesothelioma (MPeM)	Single agent: • Administer 3 mg/kg intravenously or 240 mg intravenously every 2 weeks until disease progression or unacceptable toxicity
Malignant Pleural Mesothelioma (MPM)	Single agent: o Administer 3 mg/kg intravenously or 240 mg intravenously every 2 weeks until disease progression or unacceptable toxicity In combination with ipilimumab: • Initial Therapy o Administer 360 mg intravenously every 3 weeks or 3 mg/kg every 2 weeks (given in combination with ipilimumab every 6 weeks) until disease progression or unacceptable toxicity for up to 2 years • Subsequent Therapy

	○ Administer 3 mg/kg intravenously every 2 weeks (given in combination with ipilimumab every 6 weeks) until disease progression or unacceptable toxicity; **OR** ○ Administer 240 mg intravenously every 2 weeks (given in combination with ipilimumab every 6 weeks) until disease progression or unacceptable toxicity
Cutaneous Melanoma	Adult patients and pediatric patients ≥ 12 years and ≥ 40 kg: Single agent • Unresectable or metastatic disease: Administer 240 mg intravenously every 2 weeks or 480 mg intravenously every 4 weeks until disease progression or unacceptable toxicity • Adjuvant treatment: Administer 240 mg intravenously every 2 weeks or 480 mg intravenously every 4 weeks until disease recurrence or unacceptable toxicity for up to 1 year In combination with ipilimumab • Unresectable or metastatic disease: Administer 1 mg/kg intravenously every 3 weeks for 4 doses (given in combination with ipilimumab on the same day), then follow with the single agent regimen • Adjuvant treatment: Administer 1 mg/kg intravenously every 3 weeks for 4 doses (given in combination with ipilimumab on the same day) • Neoadjuvant treatment: Administer 1 mg/kg intravenously every 3 weeks for up to 3 doses (given in combination with ipilimumab on the same day) Pediatric patients ≥ 12 years and < 40 kg: Single agent • Unresectable or metastatic disease: Administer 3 mg/kg intravenously every 2 weeks or 6 mg/kg intravenously every 4 weeks until disease progression or unacceptable toxicity • Adjuvant treatment: Administer 3 mg/kg intravenously every 2 weeks or 6 mg/kg intravenously every 4 weeks until disease recurrence or unacceptable toxicity for up to 1 year In combination with ipilimumab • Unresectable or metastatic disease: Administer 1 mg/kg intravenously every 3 weeks for 4 doses (given in combination with ipilimumab on the same day), then follow with the single agent regimen • Adjuvant treatment: Administer 1 mg/kg intravenously every 3 weeks for 4 doses (given in combination with ipilimumab on the same day)
Uveal Melanoma	In combination with ipilimumab: • Administer 1 mg/kg intravenously every 3 weeks for 4 doses (given in combination with ipilimumab on the same day), then 3 mg/kg intravenously every 2 weeks until disease progression or unacceptable toxicity
Merkel Cell Carcinoma	Neoadjuvant treatment: • Administer 240 mg intravenously every 2 weeks (days 1 and 15) for a total of 2 doses M1 disseminated disease: Single agent:

<table>
<tr><td></td><td>• Administer 240 mg intravenously every 2 weeks or 3 mg/kg intravenously every 2 weeks until disease progression or unacceptable toxicity
In combination with ipilimumab:
• Administer 1 mg/kg intravenously every 3 weeks for 4 doses (given in combination with ipilimumab on the same day), then follow with the single agent regimen
• Administer 3 mg/kg intravenously or 240 mg intravenously every 2 weeks (given in combination with ipilimumab every 6 weeks) until disease progression or unacceptable toxicity</td></tr>
<tr><td>Non-Small Cell Lung Cancer (NSCLC)</td><td><u>Neoadjuvant treatment in combination with platinum-doublet chemotherapy:</u>
• Administer 360 mg intravenously with platinum-doublet chemotherapy every 3 weeks for 3 cycles
<u>Single agent:</u>
• Administer 240 mg intravenously every 2 weeks or 480 mg intravenously every 4 weeks until disease progression or unacceptable toxicity
<u>In combination with ipilimumab:</u>
• Administer 360 mg intravenously every 3 weeks (given in combination with ipilimumab every 6 weeks) until disease progression or unacceptable toxicity for up to 2 years
<u>In combination with ipilimumab and platinum-doublet chemotherapy:</u>
• Administer 360 mg intravenously every 3 weeks (given in combination with ipilimumab every 6 weeks and histology-based platinum-doublet chemotherapy every 3 weeks for 2 cycles) until disease progression or unacceptable toxicity for up to 2 years.</td></tr>
<tr><td>Soft Tissue Sarcoma</td><td><u>Single agent:</u>
• Administer 480 mg intravenously every 4 weeks until disease progression or unacceptable toxicity
<u>In combination with ipilimumab:</u>
• Administer 240 mg intravenously every 2 weeks (given in combination with ipilimumab every 6 weeks) until disease progression or unacceptable toxicity</td></tr>
<tr><td>Cervical Cancer</td><td>Administer 240 mg intravenously every 2 weeks until disease progression or unacceptable toxicity for up to 2 years</td></tr>
<tr><td colspan="2"><u>Dosing should be calculated using actual body weight and not flat dosing (as applicable) based on the following:</u>
<table>
<tr><th>Frequency (days)</th><th>Dosing (mg/kg)</th><th>Weight (kg)</th><th>Dose (mg)</th></tr>
<tr><td rowspan="6">14</td><td rowspan="6">3</td><td><80</td><td>220</td></tr>
<tr><td><73</td><td>200</td></tr>
<tr><td><66</td><td>180</td></tr>
<tr><td><58</td><td>160</td></tr>
<tr><td><51</td><td>140</td></tr>
<tr><td><44</td><td>120</td></tr>
</table></td></tr>
</table>

	21	4.5	<80	340	
			<78	320	
			<73	300	
			<68	280	
			<63	260	
			<58	240	
			<53	220	
			<48	200	
			<44	180	
	28	6	<80	440	
			<77	420	
			<73	400	
			<69	380	
			<66	360	
			<62	340	
			<58	320	
			<55	300	
			<51	280	
			<47	260	
			<44	240	

Note: This information is not meant to replace clinical decision making when initiating or modifying medication therapy and should only be used as a guide. Patient-specific variables should be taken into account.

VI. Billing Code/Availability Information

HCPCS Code:

- J9299 – Injection, nivolumab, 1 mg; 1 billable unit = 1 mg

NDC(s):

- Opdivo 40 mg/4 mL single-dose vial: 00003-3772-xx
- Opdivo 100 mg/10 mL single-dose vial: 00003-3774-xx
- Opdivo 120 mg/12 mL single-dose vial: 00003-3756-xx
- Opdivo 240 mg/24 mL single-dose vial: 00003-3734-xx

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Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
C00.0	Malignant neoplasm of external upper lip
C00.1	Malignant neoplasm of external lower lip
C00.2	Malignant neoplasm of external lip, unspecified
C00.3	Malignant neoplasm of upper lip, inner aspect
C00.4	Malignant neoplasm of lower lip, inner aspect
C00.5	Malignant neoplasm of lip, unspecified, inner aspect
C00.6	Malignant neoplasm of commissure of lip, unspecified
C00.8	Malignant neoplasm of overlapping sites of lip
C00.9	Malignant neoplasm of lip, unspecified
C01	Malignant neoplasm of base of tongue
C02.0	Malignant neoplasm of dorsal surface of tongue
C02.1	Malignant neoplasm of border of tongue
C02.2	Malignant neoplasm of ventral surface of tongue
C02.3	Malignant neoplasm of anterior two-thirds of tongue, part unspecified
C02.4	Malignant neoplasm of lingual tonsil
C02.8	Malignant neoplasm of overlapping sites of tongue
C02.9	Malignant neoplasm of tongue, unspecified
C03.0	Malignant neoplasm of upper gum
C03.1	Malignant neoplasm of lower gum
C03.9	Malignant neoplasm of gum, unspecified
C04.0	Malignant neoplasm of anterior floor of mouth
C04.1	Malignant neoplasm of lateral floor of mouth
C04.8	Malignant neoplasm of overlapping sites of floor of mouth
C04.9	Malignant neoplasm of floor of mouth, unspecified
C05.0	Malignant neoplasm of hard palate
C05.1	Malignant neoplasm of soft palate
C05.8	Malignant neoplasm of overlapping sites of palate
C05.9	Malignant neoplasm of palate, unspecified

C06.0	Malignant neoplasm of cheek mucosa
C06.2	Malignant neoplasm of retromolar area
C06.80	Malignant neoplasm of overlapping sites of unspecified parts of mouth
C06.89	Malignant neoplasm of overlapping sites of other parts of mouth
C06.9	Malignant neoplasm of mouth, unspecified
C09.0	Malignant neoplasm of tonsillar fossa
C09.1	Malignant neoplasm of tonsillar pillar (anterior) (posterior)
C09.8	Malignant neoplasm of overlapping sites of tonsil
C09.9	Malignant neoplasm of tonsil, unspecified
C10.0	Malignant neoplasm of vallecula
C10.1	Malignant neoplasm of anterior surface of epiglottis
C10.2	Malignant neoplasm of lateral wall of oropharynx
C10.3	Malignant neoplasm of posterior wall of oropharynx
C10.4	Malignant neoplasm of branchial cleft
C10.8	Malignant neoplasm of overlapping sites of oropharynx
C10.9	Malignant neoplasm of oropharynx, unspecified
C12	Malignant neoplasm of pyriform sinus
C13.0	Malignant neoplasm of postcricoid region
C13.1	Malignant neoplasm of aryepiglottic fold, hypopharyngeal aspect
C13.2	Malignant neoplasm of posterior wall of hypopharynx
C13.8	Malignant neoplasm of overlapping sites of hypopharynx
C13.9	Malignant neoplasm of hypopharynx, unspecified
C14.0	Malignant neoplasm of pharynx, unspecified
C14.2	Malignant neoplasm of Waldeyer's ring
C14.8	Malignant neoplasm of overlapping sites of lip, oral cavity and pharynx
C15.3	Malignant neoplasm of upper third of esophagus
C15.4	Malignant neoplasm of middle third of esophagus
C15.5	Malignant neoplasm of lower third of esophagus
C15.8	Malignant neoplasm of overlapping sites of esophagus
C15.9	Malignant neoplasm of esophagus, unspecified
C16.0	Malignant neoplasm of cardia
C16.1	Malignant neoplasm of fundus of stomach
C16.2	Malignant neoplasm of body of stomach
C16.3	Malignant neoplasm of pyloric antrum
C16.4	Malignant neoplasm of pylorus
C16.5	Malignant neoplasm of lesser curvature of stomach, unspecified

C16.6	Malignant neoplasm of greater curvature of stomach, unspecified
C16.8	Malignant neoplasm of overlapping sites of stomach
C16.9	Malignant neoplasm of stomach, unspecified
C18.0	Malignant neoplasm of cecum
C18.1	Malignant neoplasm of appendix
C18.2	Malignant neoplasm of ascending colon
C18.3	Malignant neoplasm of hepatic flexure
C18.4	Malignant neoplasm of transverse colon
C18.5	Malignant neoplasm of splenic flexure
C18.6	Malignant neoplasm of descending colon
C18.7	Malignant neoplasm of sigmoid colon
C18.8	Malignant neoplasm of overlapping sites of colon
C18.9	Malignant neoplasm of colon, unspecified
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum
C21.8	Malignant neoplasm of overlapping sites of rectum, anus and anal canal
C22.0	Liver cell carcinoma
C22.1	Intrahepatic bile duct carcinoma
C22.8	Malignant neoplasm of liver, primary, unspecified as to type
C22.9	Malignant neoplasm of liver, not specified as primary or secondary
C23	Malignant neoplasm of gallbladder
C24.0	Malignant neoplasm of extrahepatic bile duct
C24.8	Malignant neoplasm of overlapping sites of biliary tract
C24.9	Malignant neoplasm of biliary tract, unspecified
C31.0	Malignant neoplasm of maxillary sinus
C31.1	Malignant neoplasm of ethmoidal sinus
C32.0	Malignant neoplasm of glottis
C32.1	Malignant neoplasm of supraglottis
C32.2	Malignant neoplasm of subglottis
C32.3	Malignant neoplasm of laryngeal cartilage
C32.8	Malignant neoplasm of overlapping sites of larynx
C32.9	Malignant neoplasm of larynx, unspecified
C33	Malignant neoplasm of trachea
C34.00	Malignant neoplasm of unspecified main bronchus
C34.01	Malignant neoplasm of right main bronchus
C34.02	Malignant neoplasm of left main bronchus

C34.10	Malignant neoplasm of upper lobe, unspecified bronchus or lung
C34.11	Malignant neoplasm of upper lobe, right bronchus or lung
C34.12	Malignant neoplasm of upper lobe, left bronchus or lung
C34.2	Malignant neoplasm of middle lobe, bronchus or lung
C34.30	Malignant neoplasm of lower lobe, unspecified bronchus or lung
C34.31	Malignant neoplasm of lower lobe, right bronchus or lung
C34.32	Malignant neoplasm of lower lobe, left bronchus or lung
C34.80	Malignant neoplasm of overlapping sites of unspecified bronchus and lung
C34.81	Malignant neoplasm of overlapping sites of right bronchus and lung
C34.82	Malignant neoplasm of overlapping sites of left bronchus and lung
C34.90	Malignant neoplasm of unspecified part of unspecified bronchus or lung
C34.91	Malignant neoplasm of unspecified part of right bronchus or lung
C34.92	Malignant neoplasm of unspecified part of left bronchus or lung
C40.00	Malignant neoplasm of scapula and long bones of unspecified upper limb
C40.01	Malignant neoplasm of scapula and long bones of right upper limb
C40.02	Malignant neoplasm of scapula and long bones of left upper limb
C40.10	Malignant neoplasm of short bones of unspecified upper limb
C40.11	Malignant neoplasm of short bones of right upper limb
C40.12	Malignant neoplasm of short bones of left upper limb
C40.20	Malignant neoplasm of long bones of unspecified lower limb
C40.21	Malignant neoplasm of long bones of right lower limb
C40.22	Malignant neoplasm of long bones of left lower limb
C40.30	Malignant neoplasm of short bones of unspecified lower limb
C40.31	Malignant neoplasm of short bones of right lower limb
C40.32	Malignant neoplasm of short bones of left lower limb
C40.80	Malignant neoplasm of overlapping sites of bone and articular cartilage of unspecified limb
C40.81	Malignant neoplasm of overlapping sites of bone and articular cartilage of right limb
C40.82	Malignant neoplasm of overlapping sites of bone and articular cartilage of left limb
C40.90	Malignant neoplasm of unspecified bones and articular cartilage of unspecified limb
C40.91	Malignant neoplasm of unspecified bones and articular cartilage of right limb
C40.92	Malignant neoplasm of unspecified bones and articular cartilage of left limb
C41.0	Malignant neoplasm of bones of skull and face
C41.1	Malignant neoplasm of mandible
C41.2	Malignant neoplasm of vertebral column
C41.3	Malignant neoplasm of ribs, sternum and clavicle
C41.4	Malignant neoplasm of pelvic bones, sacrum and coccyx

C41.9	Malignant neoplasm of bone and articular cartilage, unspecified
C43.0	Malignant melanoma of lip
C43.111	Malignant melanoma of right upper eyelid, including canthus
C43.112	Malignant melanoma of right lower eyelid, including canthus
C43.121	Malignant melanoma of left upper eyelid, including canthus
C43.122	Malignant melanoma of left lower eyelid, including canthus
C43.20	Malignant melanoma of unspecified ear and external auricular canal
C43.21	Malignant melanoma of right ear and external auricular canal
C43.22	Malignant melanoma of left ear and external auricular canal
C43.30	Malignant melanoma of unspecified part of face
C43.31	Malignant melanoma of nose
C43.39	Malignant melanoma of other parts of face
C43.4	Malignant melanoma of scalp and neck
C43.51	Malignant melanoma of anal skin
C43.52	Malignant melanoma of skin of breast
C43.59	Malignant melanoma of other part of trunk
C43.60	Malignant melanoma of unspecified upper limb, including shoulder
C43.61	Malignant melanoma of right upper limb, including shoulder
C43.62	Malignant melanoma of left upper limb, including shoulder
C43.70	Malignant melanoma of unspecified lower limb, including hip
C43.71	Malignant melanoma of right lower limb, including hip
C43.72	Malignant melanoma of left lower limb, including hip
C43.8	Malignant melanoma of overlapping sites of skin
C43.9	Malignant melanoma of skin, unspecified
C44.00	Unspecified malignant neoplasm of skin of lip
C44.02	Squamous cell carcinoma of skin of lip
C44.09	Other specified malignant neoplasm of skin of lip
C45.0	Mesothelioma of pleura
C45.1	Mesothelioma of peritoneum
C4A.0	Merkel cell carcinoma of lip
C4A.10	Merkel cell carcinoma of eyelid, including canthus
C4A.111	Merkel cell carcinoma of right upper eyelid, including canthus
C4A.112	Merkel cell carcinoma of right lower eyelid, including canthus
C4A.121	Merkel cell carcinoma of left upper eyelid, including canthus
C4A.122	Merkel cell carcinoma of left lower eyelid, including canthus
C4A.20	Merkel cell carcinoma of unspecified ear and external auricular canal

C4A.21	Merkel cell carcinoma of right ear and external auricular canal
C4A.22	Merkel cell carcinoma of left ear and external auricular canal
C4A.30	Merkel cell carcinoma of unspecified part of face
C4A.31	Merkel cell carcinoma of nose
C4A.39	Merkel cell carcinoma of other parts of face
C4A.4	Merkel cell carcinoma of scalp and neck
C4A.51	Merkel cell carcinoma of anal skin
C4A.52	Merkel cell carcinoma of skin of breast
C4A.59	Merkel cell carcinoma of other part of trunk
C4A.60	Merkel cell carcinoma of unspecified upper limb, including shoulder
C4A.61	Merkel cell carcinoma of right upper limb, including shoulder
C4A.62	Merkel cell carcinoma of left upper limb, including shoulder
C4A.70	Merkel cell carcinoma of unspecified lower limb, including hip
C4A.71	Merkel cell carcinoma of right lower limb, including hip
C4A.72	Merkel cell carcinoma of left lower limb, including hip
C4A.8	Merkel cell carcinoma of overlapping sites
C4A.9	Merkel cell carcinoma, unspecified
C46.0	Kaposi's sarcoma of skin
C46.1	Kaposi's sarcoma of soft tissue
C46.2	Kaposi's sarcoma of palate
C46.3	Kaposi's sarcoma of lymph nodes
C46.4	Kaposi's sarcoma of gastrointestinal sites
C46.50	Kaposi's sarcoma of unspecified lung
C46.51	Kaposi's sarcoma of right lung
C46.52	Kaposi's sarcoma of left lung
C46.7	Kaposi's sarcoma of other sites
C46.9	Kaposi's sarcoma, unspecified
C47.0	Malignant neoplasm of peripheral nerves of head, face and neck
C47.10	Malignant neoplasm of peripheral nerves of unspecified upper limb, including shoulder
C47.11	Malignant neoplasm of peripheral nerves of right upper limb, including shoulder
C47.12	Malignant neoplasm of peripheral nerves of left upper limb, including shoulder
C47.20	Malignant neoplasm of peripheral nerves of unspecified lower limb, including hip
C47.21	Malignant neoplasm of peripheral nerves of right lower limb, including hip
C47.22	Malignant neoplasm of peripheral nerves of left lower limb, including hip
C47.3	Malignant neoplasm of peripheral nerves of thorax
C47.4	Malignant neoplasm of peripheral nerves of abdomen
C47.5	Malignant neoplasm of peripheral nerves of pelvis
C47.6	Malignant neoplasm of peripheral nerves of trunk, unspecified

C47.8	Malignant neoplasm of overlapping sites of peripheral nerves and autonomic nervous system
C47.9	Malignant neoplasm of peripheral nerves and autonomic nervous system, unspecified
C48.0	Malignant neoplasm of retroperitoneum
C48.1	Malignant neoplasm of specified parts of peritoneum
C48.2	Malignant neoplasm of peritoneum, unspecified
C48.8	Malignant neoplasm of overlapping sites of retroperitoneum and peritoneum
C49.0	Malignant neoplasm of connective and soft tissue of head, face and neck
C49.10	Malignant neoplasm of connective and soft tissue of unspecified upper limb, including shoulder
C49.11	Malignant neoplasm of connective and soft tissue of right upper limb, including shoulder
C49.12	Malignant neoplasm of connective and soft tissue of left upper limb, including shoulder
C49.20	Malignant neoplasm of connective and soft tissue of unspecified lower limb, including hip
C49.21	Malignant neoplasm of connective and soft tissue of right lower limb, including hip
C49.22	Malignant neoplasm of connective and soft tissue of left lower limb, including hip
C49.3	Malignant neoplasm of connective and soft tissue of thorax
C49.4	Malignant neoplasm of connective and soft tissue of abdomen
C49.5	Malignant neoplasm of connective and soft tissue of pelvis
C49.6	Malignant neoplasm of connective and soft tissue of trunk, unspecified
C49.8	Malignant neoplasm of overlapping sites of connective and soft tissue
C49.9	Malignant neoplasm of connective and soft tissue, unspecified
C53.0	Malignant neoplasm of endocervix
C53.1	Malignant neoplasm of exocervix
C53.8	Malignant neoplasm of overlapping sites of cervix uteri
C53.9	Malignant neoplasm of cervix uteri, unspecified
C64.1	Malignant neoplasm of right kidney, except renal pelvis
C64.2	Malignant neoplasm of left kidney, except renal pelvis
C64.9	Malignant neoplasm of unspecified kidney, except renal pelvis
C65.1	Malignant neoplasm of right renal pelvis
C65.2	Malignant neoplasm of left renal pelvis
C65.9	Malignant neoplasm of unspecified renal pelvis
C66.1	Malignant neoplasm of right ureter
C66.2	Malignant neoplasm of left ureter
C66.9	Malignant neoplasm of unspecified ureter
C67.0	Malignant neoplasm of trigone of bladder
C67.1	Malignant neoplasm of dome of bladder
C67.2	Malignant neoplasm of lateral wall of bladder
C67.3	Malignant neoplasm of anterior wall of bladder
C67.4	Malignant neoplasm of posterior wall of bladder

C67.5	Malignant neoplasm of bladder neck
C67.6	Malignant neoplasm of ureteric orifice
C67.7	Malignant neoplasm of urachus
C67.8	Malignant neoplasm of overlapping sites of bladder
C67.9	Malignant neoplasm of bladder, unspecified
C68.0	Malignant neoplasm of urethra
C69.30	Malignant neoplasm of unspecified choroid
C69.31	Malignant neoplasm of right choroid
C69.32	Malignant neoplasm of left choroid
C69.40	Malignant neoplasm of unspecified ciliary body
C69.41	Malignant neoplasm of right ciliary body
C69.42	Malignant neoplasm of left ciliary body
C69.60	Malignant neoplasm of unspecified orbit
C69.61	Malignant neoplasm of right orbit
C69.62	Malignant neoplasm of left orbit
C76.0	Malignant neoplasm of head, face and neck
C77.0	Secondary and unspecified malignant neoplasm of lymph nodes of head, face and neck
C78.00	Secondary malignant neoplasm of unspecified lung
C78.01	Secondary malignant neoplasm of right lung
C78.02	Secondary malignant neoplasm of left lung
C78.6	Secondary malignant neoplasm of retroperitoneum and peritoneum
C78.7	Secondary malignant neoplasm of liver and intrahepatic bile duct
C79.31	Secondary malignant neoplasm of brain
C7A.1	Malignant poorly differentiated neuroendocrine tumors
C7B.1	Secondary Merkel cell carcinoma
C81.10	Nodular sclerosis Hodgkin lymphoma, unspecified site
C81.11	Nodular sclerosis Hodgkin lymphoma, lymph nodes of head, face, and neck
C81.12	Nodular sclerosis Hodgkin lymphoma, intrathoracic lymph nodes
C81.13	Nodular sclerosis Hodgkin lymphoma, intra-abdominal lymph nodes
C81.14	Nodular sclerosis Hodgkin lymphoma, lymph nodes of axilla and upper limb
C81.15	Nodular sclerosis Hodgkin lymphoma, lymph nodes of inguinal region and lower limb
C81.16	Nodular sclerosis Hodgkin lymphoma, intrapelvic lymph nodes
C81.17	Nodular sclerosis Hodgkin lymphoma, spleen
C81.18	Nodular sclerosis Hodgkin lymphoma, lymph nodes of multiple sites
C81.19	Nodular sclerosis Hodgkin lymphoma, extranodal and solid organ sites
C81.20	Mixed cellularity Hodgkin lymphoma, unspecified site

C81.21	Mixed cellularity Hodgkin lymphoma, lymph nodes of head, face, and neck
C81.22	Mixed cellularity Hodgkin lymphoma, intrathoracic lymph nodes
C81.23	Mixed cellularity Hodgkin lymphoma, intra-abdominal lymph nodes
C81.24	Mixed cellularity Hodgkin lymphoma, lymph nodes of axilla and upper limb
C81.25	Mixed cellularity Hodgkin lymphoma, lymph nodes of inguinal region and lower limb
C81.26	Mixed cellularity Hodgkin lymphoma, intrapelvic lymph nodes
C81.27	Mixed cellularity Hodgkin lymphoma, spleen
C81.28	Mixed cellularity Hodgkin lymphoma, lymph nodes of multiple sites
C81.29	Mixed cellularity Hodgkin lymphoma, extranodal and solid organ sites
C81.30	Lymphocyte depleted Hodgkin lymphoma, unspecified site
C81.31	Lymphocyte depleted Hodgkin lymphoma, lymph nodes of head, face, and neck
C81.32	Lymphocyte depleted Hodgkin lymphoma, intrathoracic lymph nodes
C81.33	Lymphocyte depleted Hodgkin lymphoma, intra-abdominal lymph nodes
C81.34	Lymphocyte depleted Hodgkin lymphoma, lymph nodes of axilla and upper limb
C81.35	Lymphocyte depleted Hodgkin lymphoma, lymph nodes of inguinal region and lower limb
C81.36	Lymphocyte depleted Hodgkin lymphoma, intrapelvic lymph nodes
C81.37	Lymphocyte depleted Hodgkin lymphoma, spleen
C81.38	Lymphocyte depleted Hodgkin lymphoma, lymph nodes of multiple sites
C81.39	Lymphocyte depleted Hodgkin lymphoma, extranodal and solid organ sites
C81.40	Lymphocyte-rich Hodgkin lymphoma, unspecified site
C81.41	Lymphocyte-rich Hodgkin lymphoma, lymph nodes of head, face, and neck
C81.42	Lymphocyte-rich Hodgkin lymphoma, intrathoracic lymph nodes
C81.43	Lymphocyte-rich Hodgkin lymphoma, intra-abdominal lymph nodes
C81.44	Lymphocyte-rich Hodgkin lymphoma, lymph nodes of axilla and upper limb
C81.45	Lymphocyte-rich Hodgkin lymphoma, lymph nodes of inguinal region and lower limb
C81.46	Lymphocyte-rich Hodgkin lymphoma, intrapelvic lymph nodes
C81.47	Lymphocyte-rich Hodgkin lymphoma, spleen
C81.48	Lymphocyte-rich Hodgkin lymphoma, lymph nodes of multiple sites
C81.49	Lymphocyte-rich Hodgkin lymphoma, extranodal and solid organ sites
C81.70	Other Hodgkin lymphoma unspecified site
C81.71	Other Hodgkin lymphoma lymph nodes of head, face, and neck
C81.72	Other Hodgkin lymphoma intrathoracic lymph nodes
C81.73	Other Hodgkin lymphoma intra-abdominal lymph nodes
C81.74	Other Hodgkin lymphoma lymph nodes of axilla and upper limb
C81.75	Other Hodgkin lymphoma lymph nodes of inguinal region and lower limb
C81.76	Other Hodgkin lymphoma intrapelvic lymph nodes

C81.77	Other Hodgkin lymphoma spleen
C81.78	Other Hodgkin lymphoma lymph nodes of multiple sites
C81.79	Other Hodgkin lymphoma extranodal and solid organ sites
C81.90	Hodgkin lymphoma, unspecified site
C81.91	Hodgkin lymphoma, unspecified lymph nodes of head, face, and neck
C81.92	Hodgkin lymphoma, unspecified intrathoracic lymph nodes
C81.93	Hodgkin lymphoma, unspecified intra-abdominal lymph nodes
C81.94	Hodgkin lymphoma, unspecified lymph nodes of axilla and upper limb
C81.95	Hodgkin lymphoma, unspecified lymph nodes of inguinal region and lower limb
C81.96	Hodgkin lymphoma, unspecified intrapelvic lymph nodes
C81.97	Hodgkin lymphoma, unspecified spleen
C81.98	Hodgkin lymphoma, unspecified lymph nodes of multiple sites
C81.99	Hodgkin lymphoma, unspecified extranodal and solid organ sites
D09.0	Carcinoma in situ of bladder
D37.01	Neoplasm of uncertain behavior of lip
D37.02	Neoplasm of uncertain behavior of tongue
D37.05	Neoplasm of uncertain behavior of pharynx
D37.09	Neoplasm of uncertain behavior of other specified sites of the oral cavity
D37.1	Neoplasm of uncertain behavior of stomach
D37.8	Neoplasm of uncertain behavior of other specified digestive organs
D37.9	Neoplasm of uncertain behavior of digestive organ, unspecified
D38.0	Neoplasm of uncertain behavior of larynx
D38.5	Neoplasm of uncertain behavior of other respiratory organs
D38.6	Neoplasm of uncertain behavior of respiratory organ, unspecified
Z85.00	Personal history of malignant neoplasm of unspecified digestive organ
Z85.01	Personal history of malignant neoplasm of esophagus
Z85.028	Personal history of other malignant neoplasm of stomach
Z85.118	Personal history of other malignant neoplasm of bronchus and lung
Z85.51	Personal history of malignant neoplasm of bladder
Z85.59	Personal history of malignant neoplasm of other urinary tract organ
Z85.71	Personal history of Hodgkin lymphoma
Z85.820	Personal history of malignant melanoma of skin
Z85.821	Personal history of Merkel cell carcinoma
Z85.830	Personal history of malignant neoplasm of bone
Z85.831	Personal history of malignant neoplasm of soft tissue

Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

The preceding information is intended for non-Medicare coverage determinations. Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determinations (NCDs) and/or Local Coverage Determinations (LCDs) may exist and compliance with these policies is required where applicable. Local Coverage Articles (LCAs) may also exist for claims payment purposes or to clarify benefit eligibility under Part B for drugs which may be self-administered. The following link may be used to search for NCD, LCD, or LCA documents: https://www.cms.gov/medicare-coverage-database/search.aspx. Additional indications, including any preceding information, may be applied at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCD/LCA): N/A

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
E (1)	CA, HI, NV, AS, GU, CNMI	Noridian Healthcare Solutions, LLC
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp (WPS)
6	MN, WI, IL	National Government Services, Inc. (NGS)
H (4 & 7)	LA, AR, MS, TX, OK, CO, NM	Novitas Solutions, Inc.
8	MI, IN	Wisconsin Physicians Service Insurance Corp (WPS)
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto GBA
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC