Keytruda® (pembrolizumab)
(Intravenous)

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I. Length of Authorization [1-3,5,15-17,69,15e]

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

- Bladder Cancer/Urothelial Carcinoma, Cervical, cHL, CNS metastases, Cutaneous Melanoma (in combination with ipilimumab), cSCC, Endometrial Carcinoma, Esophageal, GEJ, Gastric, HCC, MPM, MCC, MSI-H/dMMR, Mycosis Fungoides/Sezary Syndrome, NSCLC, PMBCL, RCC, SCCHN, Thymic Carcinoma, TMB-H Cancer, TNBC (recurrent unresectable or metastatic disease), and Vulvar can be authorized up to a maximum of twenty-four (24) months of therapy.
- Adjuvant therapy in Cutaneous Melanoma can be authorized up to a maximum of twelve (12) months of therapy.
- Neoadjuvant therapy in TNBC can be authorized up to a maximum of twenty-four (24) weeks of therapy.
- Adjuvant therapy in TNBC can be authorized up to a maximum of twenty-seven (27) weeks of therapy.
- Reinduction therapy in Cutaneous Melanoma can be authorized up to a maximum of twelve (12) months of therapy.

II. Dosing Limits

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

- Keytruda 100 mg/4 mL single use vial: 11 vials per 14 day supply

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

Indication	Billable Units (BU)	Per unit time (days)
Adrenal Gland Tumors (that is not MSI-H/dMMR), Bladder/Urothelial, Cervical, cHL, cSCC, Cutaneous Melanoma, Endometrial Carcinoma (that is not MSI-H/dMMR), Esophageal, GEJ, Gastric, HCC, MCC, MSI-H/dMMR, NSCLC, PMBCL, RCC, SCCHN, Thymic, TMB-H Cancer, TNBC, & Vulvar	200 BU	21 days
CNS metastases & MPM	1150 BU	14 days
MF/SS	250 BU	21 days

III. Initial Approval Criteria [1,2]

Coverage is provided in 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, nivolumab, atezolizumab, durvalumab, dostarlimab, etc.) unless otherwise specified; **AND**

Cutaneous Melanoma † ‡ Φ [1,2,22-24,15e]

- Used as first-line therapy as a single agent for unresectable or metastatic* disease; **OR**
- Used as subsequent therapy for unresectable or metastatic* disease after disease progression or maximum clinical benefit from BRAF targeted therapy (e.g., dabrafenib/trametinib, vemurafenib/cobimetinib, encorafenib/binimetinib, etc.); **AND**
  - Used as a single agent; **AND**
    - Anti-PD-1 immunotherapy was not previously used; **OR**
    - Used as re-induction therapy in patients who experienced stable disease or better after at least 24 months of pembrolizumab therapy OR a complete response after at least 6 months of pembrolizumab, but subsequently have disease progression after treatment discontinuation; **OR**
  - Used in combination with ipilimumab; **AND**
    - Used after progression on single-agent anti-PD-1 immunotherapy and combination ipilimumab/anti-PD-1 immunotherapy not previously used; **OR**
- Used as a single agent for adjuvant treatment; **AND**
  - Patient has stage III disease with lymph node involvement and has undergone complete resection

**Metastatic disease includes stage III clinical satellite/in transit metastases or local satellite/in-transit recurrence in patients with limited resectable and unresectable disease, unresectable nodal recurrence, and disseminated (unresectable) distant metastatic disease*

Gastric Cancer † ‡ Φ [1,2,39,67]

- Patient is not a surgical candidate or has unresectable, recurrent, locally advanced, or metastatic disease; **AND**
- Patient has adenocarcinoma histology; **AND**
  - Used as a single agent: **AND**
    - Tumor expresses PD-L1 (Combined Positive Score [CPS] ≥1) as determined by an FDA-approved or CLIA compliant test❖; **AND**
    - Patient progressed on or after at least two prior systemic treatments for their advanced disease which included fluoropyrimidine- and platinum-containing chemotherapy (*disease* progression *during or within 6 months after adjuvant therapy may be considered a previous line of therapy*); **AND**

        - Patients with HER-2 positive disease must have previously failed HER-2 directed therapy (e.g., trastuzumab, etc.); **OR**
    - Used in combination with trastuzumab, fluorouracil or capecitabine, and oxaliplatin or cisplatin; **AND**
        - Used as first-line therapy for HER2-positive disease

Esophageal or Gastroesophageal Junction Cancer † Φ [1,2,39,40,41,66]

- Patient is not a surgical candidate or has unresectable, recurrent, locally advanced, or metastatic disease; **AND**
    - Used in combination with oxaliplatin or cisplatin AND either fluorouracil or capecitabine **†**; **AND**
        - Used as first-line therapy; **AND**
        - Disease is not amenable to surgical resection or definitive chemoradiation; **AND**
        - Tumor expresses PD-L1 (CPS ≥ 10); **OR**
    - Used in combination with trastuzumab, fluorouracil or capecitabine, and oxaliplatin or cisplatin *(GEJ cancer only)* **†**; **AND**
        - Used as first-line therapy for HER2-positive disease; **AND**
        - Patient has adenocarcinoma; **OR**
    - Used as a single agent; **AND**
        - Patient has esophageal squamous cell carcinoma **†**; **AND**
            - Tumor expresses PD-L1 (CPS ≥ 10) as determined by an FDA-approved or CLIA compliant test**v**; **AND**
            - Patient progressed on or after at least one prior systemic treatment; **AND**
            - Patients with HER2 positive disease must have previously failed on HER2 directed therapy (e.g., trastuzumab, etc.); **OR**
        - Patient has gastroesophageal junction adenocarcinoma; **AND**
            - Tumor expresses PD-L1 (CPS ≥ 1) as determined by an FDA-approved or CLIA compliant test**v**; **AND**
            - Patient progressed on or after at least two prior systemic treatments for their advanced disease which included fluoropyrimidine- and platinum-containing chemotherapy (*disease progression during or within 6 months after adjuvant therapy may be considered a previous line of therapy*); **AND**
            - Patients with HER2 positive disease must have previously failed on HER2 directed therapy (e.g., trastuzumab, etc.)

Merkel Cell Carcinoma (MCC) † ‡ Φ [1,2,44,22e]

- Patients is at 6 months of age; **AND**
- Used as first-line therapy as a single agent; **AND**
    - Patient has recurrent disease AND both curative surgery and curative radiation therapy are not feasible **‡**; **OR**
    - Patient has recurrent locally advanced or metastatic disease **†**

Non-Small Cell Lung Cancer (NSCLC) † ‡ [1,2,25-29,120e,133e,136e]

- Used for stage III disease; **AND**

- Used as first-line therapy as a single-agent in patients who are not candidates for surgical resection or definitive chemoradiation with tumors that are expressing PD-L1 (TPS ≥1%) as determined by an FDA-approved or CLIA compliant test❖ and with no EGFR or ALK genomic tumor aberrations †; **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:
      - PD-L1 expression-positive (TPS ≥1%) tumors, as detected by an FDA or CLIA compliant test❖, that are negative for actionable molecular markers*
      - Patients with performance status (PS) 0-1 who have tumors that are negative for actionable molecular markers* and PD-L1 expression <1%
      - Patients with PS 0-1 who are positive for one of the following molecular markers: BRAF V600E mutation, NTRK1/2/3 gene fusion, or MET exon 14 skipping mutation; **AND**
    - Used in combination with:
      - Pemetrexed AND either carboplatin or cisplatin for non-squamous cell histology; **OR**
      - Carboplatin AND either paclitaxel or albumin-bound paclitaxel for squamous cell histology; **OR**
    - Used as a single agent *(for PD-L1 expression-positive tumors ONLY)* †; **OR**
  - Used as subsequent therapy; **AND**
    - Used in patients with tumors expressing PD-L1 (TPS ≥1%) as determined by an FDA-approved or CLIA compliant test❖ in patients with disease progression on or after platinum-containing chemotherapy (patients with EGFR or ALK genomic tumor aberrations should also have disease progression on FDA-approved therapy§); **AND**
      - Used as single agent therapy †; **OR**
    - Used for one of the following:
      - Patients with PS 0-1 who have ROS1 rearrangement-positive tumors and prior targeted therapy§
      - Patients with PS 0-1 who are positive for one of the following molecular markers: BRAF V600E mutation, NTRK1/2/3 gene fusion, or MET exon 14 skipping mutation; **AND**
      - Used in combination with carboplatin AND either paclitaxel or albumin-bound paclitaxel for squamous cell histology; **OR**
      - Used in combination with pemetrexed AND either carboplatin or cisplatin for non-squamous cell histology; **OR**
  - Used as continuation maintenance therapy in patients who have achieved tumor response or stable disease following initial therapy; **AND**
    - Used in combination with pemetrexed following a first-line pembrolizumab/pemetrexed/(carboplatin or cisplatin) regimen for disease of non-squamous cell histology; **OR**

- Used as a single agent following a first-line pembrolizumab/(carboplatin or cisplatin)/(paclitaxel or albumin-bound paclitaxel) regimen for disease of squamous cell histology; **OR**
- Used as a single agent following a first-line pembrolizumab monotherapy regimen

** Note: **Actionable molecular genomic biomarkers include EGFR, ALK, ROS1, BRAF, NTRK1/2/3, MET exon 14 skipping mutation, and RET rearrangement.** If there is insufficient issue to allow testing for all of EGFR, ALK, ROS1, BRAF, NTRK1/2/3, MET and RET, repeat biopsy and/or plasma testing should be done. If these are not feasible, treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes.*

Squamous Cell Carcinoma of the Head and Neck (SCCHN) † ‡ [1,2,31,32,42e]

- Used as first-line therapy for non-nasopharyngeal disease; **AND**
  - Patient is unfit for surgery or has locally advanced, unresectable, recurrent, or metastatic disease; **AND**
    - Used as a single-agent for tumors expressing PD-L1 (CPS ≥1) as determined by an FDA-approved or CLIA-compliant test❖; **OR**
    - Used in combination with fluorouracil and a platinum chemotherapy agent; **OR**
- Used as subsequent therapy; **AND**
  - Patient has locally advanced, unresectable, recurrent/persistent, or metastatic disease; **AND**
  - Used as a single-agent therapy for tumors expressing PD-L1 (CPS ≥1) for disease that has progressed on or after platinum-containing chemotherapy

Adult Classical Hodgkin Lymphoma (cHL) † Φ [1,2,33,61]

- Used as a single agent for relapsed or refractory disease

Pediatric Classical Hodgkin Lymphoma † ‡ Φ [1,2,33,61]

- Patient is at least 6 months of age; **AND**
- Used as a single agent; **AND**
  - Patient has refractory disease †; **OR**
  - Patient has relapsed disease after two or more prior lines of therapy †; **OR**
  - Used in patients heavily pretreated with platinum or anthracycline-based chemotherapy; **OR**
  - Used as subsequent therapy in patients with an observed decrease in cardiac function

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

Primary Mediastinal Large B-Cell Lymphoma (PMBCL) † ‡ Φ [1,2,34]

- Patient is at least 6 months of age; **AND**
- Used as single agent; **AND**
- Patient has relapsed or refractory disease; **AND**
- Patient does not require urgent cytoreductive therapy; **AND**
- Used after autologous stem-cell transplant OR if ineligible for autologous stem-cell transplant, used after 2 or more prior lines of therapy

Urothelial Carcinoma (Bladder Cancer) † ‡ [1,2,8,35-37,54e-55e]

- Used as a single agent; **AND**

- Patient has Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) defined as one of the following:
  - Persistent disease despite adequate BCG therapy**; **OR**
  - Disease recurrence after an initial tumor free state following an adequate BCG course of therapy**; **OR**
  - T1 disease following a single induction course of BCG therapy; **AND**
  - Patient has carcinoma in situ (CIS); **AND**
  - Patient is ineligible for or has elected not to undergo cystectomy; **OR**
- Patient has one of the following diagnoses:
  - Locally advanced or metastatic urothelial carcinoma; **OR**
  - Muscle invasive bladder cancer with local recurrence or persistent disease in a preserved bladder; **OR**
  - Metastatic or local bladder cancer recurrence post-cystectomy; **OR**
  - Primary carcinoma of the urethra; **AND**
    - Used for metastatic or recurrent disease *(excluding recurrence of stage T3-4 disease or palpable inguinal lymph nodes)*; **OR**
    - Used for clinical stage T3-4 cN1-2 disease or cN1-2 palpable inguinal lymph nodes *(first-line therapy only)*; **OR**
  - Metastatic upper genitourinary (GU) tract tumors; **OR**
  - Metastatic urothelial carcinoma of the prostate; **AND**
  - Used for disease that progressed during or following platinum-containing chemotherapy*; **OR**
  - Used as first-line therapy in cisplatin-ineligible patients*; **AND**
    - Patient is carboplatin-ineligible*; **OR**
    - Tumors express PD-L1 (CPS ≥10) as determined by an FDA-approved or CLIA-compliant test❖

** Adequate BCG therapy is defined as administration of at least five of six doses of an initial induction course AND at least two of three doses of maintenance therapy or at least two of six doses of a second induction course*

**** Note:*** [10,18]

- *If platinum treatment occurred greater than 12 months ago, the patient should be re-treated with platinum-based therapy if the patient is still platinum eligible (see below for cisplatin- or carboplatin-ineligible comorbidities).*
  - *Cisplatin-ineligible comorbidities may include the following: GFR < 60 mL/min, PS ≥ 2, hearing loss of ≥ 25 decibels (dB) at two contiguous frequencies, or grades ≥ 2 peripheral neuropathy. Carboplatin may be substituted for cisplatin particularly in those patients with a GFR <60 mL/min or a PS of 2.*
  - *Carboplatin-ineligible comorbidities may include the following: GFR < 30 mL/min, PS ≥ 3, grade ≥ 3 peripheral neuropathy, or NYHA class ≥ 3, etc.*

Cervical Cancer † ‡ [1,2,42]

- Used as a single agent; **AND**
- Patient has persistent, recurrent, or metastatic disease; **AND**

- Tumor expresses PD-L1 (e.g., CPS ≥1) as determined by an FDA-approved or CLIA-compliant test❖; **AND**
- Disease has progressed on or after chemotherapy

Microsatellite Instability-High (MSI-H) Cancer † ‡ [1,2,4,38,51]

- Patient at least 6 months of age; **AND**
- Used as a single agent; **AND**
- Patient's disease must be microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR); **AND**
- Pediatric patients must not have a diagnosis of MSI-H central nervous system cancer; **AND**
- Patient has one of the following cancers:
  - Colorectal Cancer † ‡ [38]
    - Used for previously untreated unresectable or metastatic disease; **OR**
    - Used for unresectable, advanced, or metastatic disease that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan
  - Pancreatic Adenocarcinoma ‡ [60e]
    - Used as subsequent therapy for locally advanced or metastatic disease after progression
  - Bone Cancer (Chondrosarcoma *[excluding dedifferentiated or mesenchymal subtypes]* or Osteosarcoma *[excluding high-grade undifferentiated pleomorphic sarcoma]*) ‡
    - Used for unresectable or metastatic disease that has progressed following prior treatment; **AND**
    - Patient has no satisfactory alternative treatment options
  - Gastric Adenocarcinoma OR Esophageal/Gastroesophageal Junction Adenocarcinoma or Squamous Cell Carcinoma ‡
    - Used as subsequent therapy for patients who are not surgical candidates or have unresectable locally advanced, recurrent, or metastatic disease
  - Ovarian Cancer (epithelial ovarian, fallopian tube, and primary peritoneal cancers) ‡
    - Patient has carcinosarcoma (i.e., malignant mixed Müllerian tumor [MMMT]), clear cell, endometrioid, mucinous, or serous histology; **AND**
    - Used for patients with persistent or recurrent disease; **AND**
    - Patient is not experiencing an immediate biochemical relapse (i.e., rising CA-125 with no radiographic evidence of disease)
  - Uterine Cancer (endometrial carcinoma) ‡
    - Used as second-line therapy for recurrent, metastatic, or high-risk disease that has progressed following prior treatment
  - Hepatobiliary Adenocarcinoma (intra-/extra-hepatic cholangiocarcinoma) ‡ [60e]
    - Used for unresectable or metastatic disease that has progressed following prior treatment
  - Cervical Cancer ‡
    - Used as second-line therapy for persistent, recurrent, or metastatic disease
  - Small Bowel Adenocarcinoma ‡ [2,60e]
    - Used for advanced or metastatic disease; **AND**
    - Used as subsequent therapy in patients without a contraindication to oxaliplatin
  - Breast Cancer ‡
    - Used for recurrent unresectable or metastatic disease; **AND**
    - Patient has progressed following prior treatment; **AND**

        - Patient has no satisfactory alternative treatment options
    - Prostate Cancer ‡
        - Patient has castration-resistant metastatic disease; **AND**
        - Patient will continue androgen deprivation therapy (ADT); **AND**
            - Patient received prior docetaxel and no prior novel hormone therapy; **OR**
            - Patient received prior novel hormone therapy and no prior docetaxel; **OR**
            - Patient received prior docetaxel and prior novel hormone therapy *(excluding patients with visceral metastases)*
    - Neuroendocrine Tumors (Poorly differentiated neuroendocrine carcinoma, poorly differentiated unknown primary, or large or small cell carcinoma [other than lung])
        - Patient progressed following prior treatment and has no satisfactory alternative treatment options

Thymic Carcinoma ‡ [2,16,17]

- Used as a single agent; **AND**
- Used as second-line therapy for unresectable or metastatic disease

Malignant Pleural Mesothelioma (MPM) ‡ [2,3]

- Used as subsequent therapy as a single agent

Central Nervous System (CNS) Cancer ‡ [2,47,50]

- Used as single agent therapy; **AND**
- Primary tumor is due to melanoma or PD-L1 positive non-small cell lung cancer (NSCLC); **AND**
    - Used as initial treatment in patients with small asymptomatic brain metastases; **OR**
    - Used for relapsed disease in patients with limited brain metastases and stable systemic disease or reasonable treatment options; **OR**
    - Patient has recurrent limited brain metastases; **OR**
    - Used for recurrent disease in patients with extensive brain metastases and stable systemic disease or reasonable systemic treatment options

Hepatocellular Carcinoma (HCC) † Φ [1,2,43]

- Used as a single agent; **AND**
- Patient was previously treated with sorafenib; **AND**
- Patient has Child-Pugh Class A liver impairment *(i.e., excluding Child-Pugh Class B and C)*

Mycosis Fungoides/Sezary Syndrome ‡ [2,15,102e,104e,117e]

- Used for relapsed or persistent disease; **AND**
    - Patient has stage III Mycosis Fungoides; **OR**
    - Patient has stage IV Sezary Syndrome; **OR**
- Used for disease refractory to multiple previous therapies

Renal Cell Carcinoma (RCC) † [1,2,45]

- Patient has clear cell histology; **AND**
    - Used in combination with axitinib; **AND**

        - Used as first-line therapy for advanced, relapsed, or stage IV disease; **OR**
    - Used in combination with lenvatinib ‡; **AND**
        - Used as first-line therapy for relapsed or stage IV disease; **OR**
- Patient has non-clear cell histology; **AND**
    - Used as a single agent as first-line therapy for relapsed or stage IV disease ‡

Endometrial Carcinoma (Uterine Cancer) † ‡ [1,2,46]

- Patient has advanced or recurrent disease; **AND**
- Patient has disease progression following prior systemic therapy; **AND**
- Patient is not a candidate for curative surgery or radiation; **AND**
- Used in combination with lenvatinib

Tumor Mutational Burden-High (TMB-H) Cancer † ‡ [1,2,57]

- Patient is at least 6 months of age; **AND**
- Patient has tumor mutational burden-high (TMB-H) [≥ 10 mutations/megabase (mut/Mb)] solid tumors as determined by an FDA-approved or CLIA-compliant test❖; **AND**
- Used as a single agent; **AND**
- Pediatric patients must not have a diagnosis of TMB-H central nervous system cancer; **AND**
- Patient does not have melanoma or non-small cell lung cancer (NSCLC); **AND**
- Patient has one of the following cancers:
    - Cervical Cancer ‡
        - Used as second-line therapy for unresectable or metastatic disease; **AND**
        - Patient has no satisfactory alternative treatment options
    - Salivary Gland Tumors ‡
        - Used for recurrent metastatic disease in patients with a PS 0-3; **OR**
        - Used for unresectable locoregional recurrence or second primary with prior radiation therapy
    - Thyroid Carcinoma ‡
        - Anaplastic Carcinoma
            - Used as second-line therapy for metastatic disease
        - Follicular Carcinoma, Papillary Carcinoma, Hürthle Cell Carcinoma
            - Patient has unresectable locoregional recurrent/persistent, or metastatic disease not amenable to radioactive iodine (RAI) therapy
        - Medullary Carcinoma
            - Patient has unresectable locoregional or recurrent/persistent metastatic disease
    - Uterine Cancer *(excluding sarcomas and mesenchymal tumors)* ‡
        - Used as second-line therapy for unresectable or metastatic disease that progressed following prior treatment; **AND**
        - Patient has no satisfactory alternative treatment options
    - Vulvar Squamous Cell Carcinoma
        - Used for advanced, recurrent, or metastatic disease as second-line therapy; **AND**
        - Patient has no satisfactory alternative treatment options
    - Well-Differentiated Grade 3 Neuroendocrine Tumors ‡

- Patient has locally advanced or metastatic disease with unfavorable biology (e.g., relative high Ki-67 [≥55%], rapid growth rate, negative SSR-based PET imaging); **AND**
- Patient progressed following prior treatment and has no satisfactory alternative treatment options

- Neuroendocrine Tumors (Poorly differentiated neuroendocrine carcinoma, poorly differentiated unknown primary, or large or small cell carcinoma [other than lung]) ‡
  - Patient progressed following prior treatment and has no satisfactory alternative treatment options

Cutaneous Squamous Cell Carcinoma (cSCC) † [1,58,125e]

- Used as a single agent and one of the following:
  - Patient has recurrent or metastatic disease that is not curable by surgery or radiation; **OR**
  - Patient has locally advanced disease that is not curable by surgery or radiation

Adrenal Gland Tumors ‡ [2,62,63,128e,129e]

- Patient has locoregional unresectable or metastatic adrenocortical carcinoma (ACC); **AND**
- Used with or without mitotane

Triple Negative Breast Cancer (TNBC) † ‡ [1,69]

- Used as first-line therapy for recurrent unresectable or metastatic disease; **AND**
  - Used in combination with albumin-bound paclitaxel, paclitaxel, or gemcitabine with carboplatin; **AND**
  - Tumor expresses PD-L1 (CPS ≥10) as determined by an FDA-approved or CLIA-compliant test❖; **OR**
- Patient has high-risk early-stage disease; **AND**
  - Used as neoadjuvant therapy in combination with chemotherapy; **OR**
  - Used as adjuvant therapy as a single agent

❖ *If confirmed using an immunotherapy assay-http://www.fda.gov/companiondiagnostics*

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.

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

Genomic Aberration/Mutational Driver Targeted Therapies (Note: *not all inclusive, refer to guidelines for appropriate use*) §				
Sensitizing *EGFR* mutation-positive tumors	*ALK* rearrangement-positive tumors	*ROS1* rearrangement-positive tumors	*BRAF* V600E-mutation positive tumors	*NTRK* Gene Fusion positive tumors
– Afatinib – Erlotinib – Dacomitinib – Gefitinib – Osimertinib – Amivantamab *(exon-20 insertion)*	– Alectinib – Brigatinib – Ceritinib – Crizotinib – Lorlatinib	– Ceritinib – Crizotinib – Entrectinib	– Dabrafenib ± Trametinib – Vemurafenib	– Larotrectinib – Entrectinib

PD-1/PD-L1 expression-positive tumors (≥1%)	*MET* Exon-14 skipping mutations	*RET* rearrangement-positive tumors	KRAS G12C mutations	
– Pembrolizumab – Atezolizumab – Nivolumab ± ipilimumab	– Capmatinib – Crizotinib – Tepotinib	– Selpercatinib – Cabozantinib – Vandetanib – Pralsetinib	– Sotorasib	

IV. Renewal Criteria [1-3,5,15-17,15e]

Coverage can be renewed based upon the following criteria:

- Patient continues to meet universal and other indication-specific relevant criteria identified in section III; **AND**
- Disease response with treatment as defined by stabilization of disease or decrease in size of tumor or tumor spread; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: severe infusion reactions, severe immune-mediated adverse reactions (e.g., pneumonitis, hepatitis, colitis, endocrinopathies, nephritis and renal dysfunction, dermatologic adverse reactions/rashes, etc.), hepatotoxicity when used in combination with axitinib, etc.; **AND**
- For the following indications, patient has not exceeded a maximum of twenty-four (24) months of therapy:
  - Bladder Cancer/Urothelial Carcinoma
  - Cervical Cancer
  - Classical Hodgkin Lymphoma (cHL)
  - CNS Metastases
  - Cutaneous Melanoma (in combination with ipilimumab only)
  - Cutaneous Squamous Cell Carcinoma (cSCC)
  - Endometrial Carcinoma
  - Esophageal/Gastroesophageal Cancer
  - Gastric Cancer
  - Hepatocellular Carcinoma (HCC)
  - Malignant Pleural Mesothelioma (MPM)
  - Merkel Cell Carcinoma (MCC)
  - MSI-H/dMMR Cancer
  - Mycosis Fungoides/Sezary Syndrome
  - Non-Small Cell Lung Cancer (NSCLC)
  - Primary Mediastinal Large B-Cell Lymphoma (PMBCL)
  - Renal Cell Carcinoma (RCC)
  - Squamous Cell Carcinoma of the Head and Neck (SCCHN)
  - Thymic Carcinoma
  - Tumor Mutational Burden-High Cancer
  - Triple Negative Breast Cancer (recurrent unresectable or metastatic disease)

Cutaneous Melanoma (adjuvant treatment or re-induction therapy)

- Patient has not exceeded a maximum of twelve (12) months of therapy

Cutaneous Melanoma (subsequent treatment after prior anti-PD-1 immunotherapy) ‡

- *Refer to Section III for criteria*

Triple Negative Breast Cancer (neoadjuvant treatment)

- Patient has not exceeded a maximum of twenty-four (24) weeks of therapy

Triple Negative Breast Cancer (adjuvant treatment)

- Patient has not exceeded a maximum of twenty-seven (27) weeks of therapy

Continuation Maintenance Therapy for NSCLC

- *Refer to Section III for criteria*

V. Dosage/Administration [1-6,8,12,13,15-17,22-48,50-55,15e]

Indication	Dose
Bladder Cancer/Urothelial Carcinoma, Cervical, cSCC, Endometrial Carcinoma (that is NOT MSI-H/dMMR), Esophageal, GEJ, Gastric, HCC, NSCLC, RCC, SCCHN, & TNBC (recurrent unresectable or metastatic disease)	200 mg intravenously every 3 weeks or 400 mg intravenously every 6 weeks up to a maximum of 24 months in patients without disease progression or unacceptable toxicity **NMIBC treatment may continue up to a maximum of 24 months in patients without persistent or recurrent disease, disease progression, or unacceptable toxicity.*
TNBC (neoadjuvant or adjuvant therapy)	Neoadjuvant therapy: 200 mg intravenously every 3 weeks or 400 mg intravenously every 6 weeks up to a maximum of 24 weeks in patients without disease progression or unacceptable toxicity (up to 8 doses of 200 mg every 3 weeks or 4 doses of 400 mg every 6 weeks) Adjuvant therapy*: 200 mg intravenously every 3 weeks or 400 mg intravenously every 6 weeks up to a maximum of 27 weeks in patients without disease progression or unacceptable toxicity (up to 9 doses of 200 mg every 3 weeks or 5 doses of 400 mg every 6 weeks) ** Patients who experience disease progression or unacceptable toxicity related to KEYTRUDA with neoadjuvant treatment in combination with chemotherapy should not receive adjuvant single agent KEYTRUDA.*
Thymic Carcinoma	200 mg intravenously every 3 weeks up to a maximum of 24 months in patients without disease progression or unacceptable toxicity
Cutaneous Melanoma	Single agent therapy *(excluding adjuvant treatment or re-induction therapy)*: 200 mg intravenously every 3 weeks or 400 mg intravenously every 6 weeks until disease progression or unacceptable toxicity In combination with ipilimumab: 200 mg intravenously every 3 weeks up to a maximum of 24 months in patients without disease progression or unacceptable toxicity Adjuvant treatment or re-induction therapy:

	200 mg intravenously every 3 weeks or 400 mg intravenously every 6 weeks up to a maximum of 12 months in patients without disease recurrence or unacceptable toxicity
cHL, MCC, MSI-H/dMMR Cancer, PMBCL, & TMB-H Cancer	Adults*: 200 mg intravenously every 3 weeks or 400 mg intravenously every 6 weeks Pediatrics*: 2 mg/kg (up to 200 mg) intravenously every 21 days **Up to a maximum of 24 months in patients without disease progression or unacceptable toxicity*
CNS metastases & MPM	10 mg/kg intravenously every 2 weeks for up to 24 months or until confirmed progression or unacceptable toxicity
MF/SS	2 mg/kg intravenously every 3 weeks up to a maximum of 24 months in patients without disease progression or unacceptable toxicity
Adrenal Gland Tumors (that is NOT MSI-H/dMMR)	200 mg intravenously every 3 weeks

Dosing should be calculated using actual body weight and not flat dosing (as applicable) based on the following:

- Standard dose 200 mg IV every 3 weeks for patients > 50 kg
- Use 100 mg IV every 3 weeks for patients ≤ 50 kg

-OR-

- Standard dose 400 mg IV every 6 weeks for patients weighing > 82.5 kg
- Use 300 mg IV every 6 weeks for patients weighing between 56 to 82.5 kg
- Use 200 mg IV every 6 weeks for patients weighing ≤ 55 kg

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:

- J9271 – Injection, pembrolizumab, 1 mg; 1 billable unit = 1 mg

NDC:

- Keytruda 100 mg/4 mL single use vial: 00006-3026-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

ICD-10	ICD-10 Description
C07	Malignant neoplasm of parotid gland
C08.0	Malignant neoplasm of submandibular gland
C08.1	Malignant neoplasm of sublingual gland
C08.9	Malignant neoplasm of major salivary gland, 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
C17.0	Malignant neoplasm of duodenum

ICD-10	ICD-10 Description
C17.1	Malignant neoplasm of jejunum
C17.2	Malignant neoplasm of ileum
C17.3	Meckel's diverticulum, malignant
C17.8	Malignant neoplasm of overlapping sites of small intestine
C17.9	Malignant neoplasm of small intestine, 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
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
C25.0	Malignant neoplasm of head of pancreas
C25.1	Malignant neoplasm of body of the pancreas
C25.2	Malignant neoplasm of tail of pancreas
C25.3	Malignant neoplasm of pancreatic duct
C25.7	Malignant neoplasm of other parts of pancreas
C25.8	Malignant neoplasm of overlapping sites of pancreas
C25.9	Malignant neoplasm of pancreas, 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

ICD-10	ICD-10 Description
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
C37	Malignant neoplasm of thymus
C38.4	Malignant neoplasm of pleura
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

ICD-10	ICD-10 Description
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
C43.10	Malignant melanoma of unspecified eyelid, including canthus
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
C44.121	Squamous cell carcinoma of skin of unspecified eyelid, including canthus
C44.1221	Squamous cell carcinoma of skin of right upper eyelid, including canthus
C44.1222	Squamous cell carcinoma of skin of right lower eyelid, including canthus
C44.1291	Squamous cell carcinoma of skin of left upper eyelid, including canthus
C44.1292	Squamous cell carcinoma of skin of left lower eyelid, including canthus
C44.221	Squamous cell carcinoma of skin of unspecified ear and external auricular canal
C44.222	Squamous cell carcinoma of skin of right ear and external auricular canal

ICD-10	ICD-10 Description
C44.229	Squamous cell carcinoma of skin of left ear and external auricular canal
C44.320	Squamous cell carcinoma of skin of unspecified parts of face
C44.321	Squamous cell carcinoma of skin of nose
C44.329	Squamous cell carcinoma of skin of other parts of face
C44.42	Squamous cell carcinoma of skin of scalp and neck
C44.520	Squamous cell carcinoma of anal skin
C44.521	Squamous cell carcinoma of skin of breast
C44.529	Squamous cell carcinoma of skin of other part of trunk
C44.621	Squamous cell carcinoma of skin of unspecified upper limb, including shoulder
C44.622	Squamous cell carcinoma of skin of right upper limb, including shoulder
C44.629	Squamous cell carcinoma of skin of left upper limb, including shoulder
C44.721	Squamous cell carcinoma of skin of unspecified lower limb, including hip
C44.722	Squamous cell carcinoma of skin of right lower limb, including hip
C44.729	Squamous cell carcinoma of skin of left lower limb, including hip
C44.82	Squamous cell carcinoma of overlapping sites of skin
C44.92	Squamous cell carcinoma of skin, unspecified
C45.0	Mesothelioma of pleura
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

ICD-10	ICD-10 Description
C4A.8	Merkel cell carcinoma of overlapping sites
C4A.9	Merkel cell carcinoma, unspecified
C50.011	Malignant neoplasm of nipple and areola, right female breast
C50.012	Malignant neoplasm of nipple and areola, left female breast
C50.019	Malignant neoplasm of nipple and areola, unspecified female breast
C50.021	Malignant neoplasm of nipple and areola, right male breast
C50.022	Malignant neoplasm of nipple and areola, left male breast
C50.029	Malignant neoplasm of nipple and areola, unspecified male breast
C50.111	Malignant neoplasm of central portion of right female breast
C50.112	Malignant neoplasm of central portion of left female breast
C50.119	Malignant neoplasm of central portion of unspecified female breast
C50.121	Malignant neoplasm of central portion of right male breast
C50.122	Malignant neoplasm of central portion of left male breast
C50.129	Malignant neoplasm of central portion of unspecified male breast
C50.211	Malignant neoplasm of upper-inner quadrant of right female breast
C50.212	Malignant neoplasm of upper-inner quadrant of left female breast
C50.219	Malignant neoplasm of upper-inner quadrant of unspecified female breast
C50.221	Malignant neoplasm of upper-inner quadrant of right male breast
C50.222	Malignant neoplasm of upper-inner quadrant of left male breast
C50.229	Malignant neoplasm of upper-inner quadrant of unspecified male breast
C50.311	Malignant neoplasm of lower-inner quadrant of right female breast
C50.312	Malignant neoplasm of lower-inner quadrant of left female breast
C50.319	Malignant neoplasm of lower-inner quadrant of unspecified female breast
C50.321	Malignant neoplasm of lower-inner quadrant of right male breast
C50.322	Malignant neoplasm of lower-inner quadrant of left male breast
C50.329	Malignant neoplasm of lower-inner quadrant of unspecified male breast
C50.411	Malignant neoplasm of upper-outer quadrant of right female breast
C50.412	Malignant neoplasm of upper-outer quadrant of left female breast
C50.419	Malignant neoplasm of upper-outer quadrant of unspecified female breast
C50.421	Malignant neoplasm of upper-outer quadrant of right male breast
C50.422	Malignant neoplasm of upper-outer quadrant of left male breast
C50.429	Malignant neoplasm of upper-outer quadrant of unspecified male breast
C50.511	Malignant neoplasm of lower-outer quadrant of right female breast
C50.512	Malignant neoplasm of lower-outer quadrant of left female breast
C50.519	Malignant neoplasm of lower-outer quadrant of unspecified female breast
C50.521	Malignant neoplasm of lower-outer quadrant of right male breast
C50.522	Malignant neoplasm of lower-outer quadrant of left male breast
C50.529	Malignant neoplasm of lower-outer quadrant of unspecified male breast
C50.611	Malignant neoplasm of axillary tail of right female breast

ICD-10	ICD-10 Description
C50.612	Malignant neoplasm of axillary tail of left female breast
C50.619	Malignant neoplasm of axillary tail of unspecified female breast
C50.621	Malignant neoplasm of axillary tail of right male breast
C50.622	Malignant neoplasm of axillary tail of left male breast
C50.629	Malignant neoplasm of axillary tail of unspecified male breast
C50.811	Malignant neoplasm of overlapping sites of right female breast
C50.812	Malignant neoplasm of overlapping sites of left female breast
C50.819	Malignant neoplasm of overlapping sites of unspecified female breast
C50.821	Malignant neoplasm of overlapping sites of right male breast
C50.822	Malignant neoplasm of overlapping sites of left male breast
C50.829	Malignant neoplasm of overlapping sites of unspecified male breast
C50.911	Malignant neoplasm of unspecified site of right female breast
C50.912	Malignant neoplasm of unspecified site of left female breast
C50.919	Malignant neoplasm of unspecified site of unspecified female breast
C50.921	Malignant neoplasm of unspecified site of right male breast
C50.922	Malignant neoplasm of unspecified site of left male breast
C50.929	Malignant neoplasm of unspecified site of unspecified male breast
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
C54.0	Malignant neoplasm of isthmus uteri
C54.1	Malignant neoplasm of endometrium
C54.2	Malignant neoplasm of myometrium
C54.3	Malignant neoplasm of fundus uteri
C54.8	Malignant neoplasm of overlapping sites of corpus uteri
C54.9	Malignant neoplasm of corpus uteri, unspecified
C55	Malignant neoplasm of uterus, part unspecified
C56.1	Malignant neoplasm of right ovary
C56.2	Malignant neoplasm of left ovary
C56.9	Malignant neoplasm of unspecified ovary
C57.00	Malignant neoplasm of unspecified fallopian tube
C57.01	Malignant neoplasm of right fallopian tube
C57.02	Malignant neoplasm of left fallopian tube
C57.10	Malignant neoplasm of unspecified broad ligament
C57.11	Malignant neoplasm of right broad ligament
C57.12	Malignant neoplasm of left broad ligament
C57.20	Malignant neoplasm of unspecified round ligament
C57.21	Malignant neoplasm of right round ligament

ICD-10	ICD-10 Description
C57.22	Malignant neoplasm of left round ligament
C57.3	Malignant neoplasm of parametrium
C57.4	Malignant neoplasm of uterine adnexa, unspecified
C57.7	Malignant neoplasm of other specified female genital organs
C57.8	Malignant neoplasm of overlapping sites of female genital organs
C57.9	Malignant neoplasm of female genital organ, unspecified
C61	Malignant neoplasm of prostate
C63.2	Malignant neoplasm of scrotum
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
C74.00	Malignant neoplasm of cortex of unspecified adrenal gland
C74.01	Malignant neoplasm of cortex of right adrenal gland
C74.02	Malignant neoplasm of cortex of left adrenal gland
C74.90	Malignant neoplasm of unspecified part of unspecified adrenal gland
C74.91	Malignant neoplasm of unspecified part of right adrenal gland
C74.92	Malignant neoplasm of unspecified part of left adrenal gland
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

ICD-10	ICD-10 Description
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
C79.51	Secondary malignant neoplasm of bone
C79.52	Secondary malignant neoplasm of bone marrow
C7A.1	Malignant poorly differentiated neuroendocrine tumors
C7A.8	Other malignant neuroendocrine tumors
C7B.00	Secondary carcinoid tumors unspecified site
C7B.01	Secondary carcinoid tumors of distant lymph nodes
C7B.02	Secondary carcinoid tumors of liver
C7B.03	Secondary carcinoid tumors of bone
C7B.04	Secondary carcinoid tumors of peritoneum
C7B.1	Secondary Merkel cell carcinoma
C7B.8	Other secondary neuroendocrine tumors
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

ICD-10	ICD-10 Description
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, 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
C84.00	Mycosis fungoides, unspecified site
C84.01	Mycosis fungoides, lymph nodes of head, face, and neck
C84.02	Mycosis fungoides, intrathoracic lymph nodes
C84.03	Mycosis fungoides, intra-abdominal lymph nodes

ICD-10	ICD-10 Description
C84.04	Mycosis fungoides, lymph nodes of axilla and upper limb
C84.05	Mycosis fungoides, lymph nodes of inguinal region and lower limb
C84.06	Mycosis fungoides, intrapelvic lymph nodes
C84.07	Mycosis fungoides, spleen
C84.08	Mycosis fungoides, lymph nodes of multiple sites
C84.09	Mycosis fungoides, extranodal and solid organ sites
C84.10	Sézary disease, unspecified site
C84.11	Sézary disease, lymph nodes of head, face, and neck
C84.12	Sézary disease, intrathoracic lymph nodes
C84.13	Sézary disease, intra-abdominal lymph nodes
C84.14	Sézary disease, lymph nodes of axilla and upper limb
C84.15	Sézary disease, lymph nodes of inguinal region and lower limb
C84.16	Sézary disease, intrapelvic lymph nodes
C84.17	Sézary disease, spleen
C84.18	Sézary disease, lymph nodes of multiple sites
C84.19	Sézary disease, extranodal and solid organ sites
C85.20	Mediastinal (thymic) large B-cell lymphoma, unspecified site
C85.21	Mediastinal (thymic) large B-cell lymphoma, lymph nodes of head, face and neck
C85.22	Mediastinal (thymic) large B-cell lymphoma, intrathoracic lymph nodes
C85.23	Mediastinal (thymic) large B-cell lymphoma, intra-abdominal lymph nodes
C85.24	Mediastinal (thymic) large B-cell lymphoma, lymph nodes of axilla and upper limb
C85.25	Mediastinal (thymic) large B-cell lymphoma, lymph nodes of inguinal region and lower limb
C85.26	Mediastinal (thymic) large B-cell lymphoma, intrapelvic lymph nodes
C85.27	Mediastinal (thymic) large B-cell lymphoma, spleen
C85.28	Mediastinal (thymic) large B-cell lymphoma, lymph nodes of multiple sites
C85.29	Mediastinal (thymic) large B-cell lymphoma, extranodal and solid organ sites
D09.0	Carcinoma in situ of bladder
D15.0	Benign neoplasm of other and unspecified intrathoracic organs
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

ICD-10	ICD-10 Description
Z85.01	Personal history of malignant neoplasm of esophagus
Z85.028	Personal history of other malignant neoplasm of stomach
Z85.038	Personal history of other malignant neoplasm of large intestine
Z85.068	Personal history of other malignant neoplasm of small intestine
Z85.118	Personal history of other malignant neoplasm of bronchus and lung
Z85.51	Personal history of malignant neoplasm of bladder
Z85.528	Personal history of other malignant neoplasm of kidney
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
Z85.830	Personal history of malignant neoplasm of bone
Z85.858	Personal history of malignant neoplasm of other endocrine glands

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

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 Determination (NCD), Local Coverage Determinations (LCDs), and Local Coverage Articles (LCAs) may exist and compliance with these policies is required where applicable. They can be found at: http://www.cms.gov/medicare-coverage-database/search/advanced-search.aspx. Additional indications may be covered 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, LLC
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA, LLC
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA)	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC

Appendix 3 – CLINICAL LITERATURE REVIEW

OS = overall survival; PFS = progression-free survival; ORR = objective response rate; CR = complete response; PR = partial response; SD = stable disease; DoR = duration of response; TTP = time to progression; FFS = failure-free survival; EFS = event-free survival; PFR = progression free rate; RFS = recurrence-free survival; DMFS = distant metastases-free survival; DCR = disease control rate; CPS = combined positive score; SCC = squamous cell carcinoma; ASCT = autologous stem cell transplant; NR = not reached; NPR – non-progression rate

Cutaneous Melanoma

First-line therapy for unresectable or metastatic disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pembrolizumab (10 mg/kg every 2 weeks or 10 mg/kg every 3 weeks)	1 preferred	Yes	Phase 3 (KEYNOTE-006), randomized, open-label, multi-center, active-controlled trial	Ipilimumab (4 doses unless discontinued earlier for disease progression or unacceptable toxicity)	PFS OS	First- or second-line therapy (no prior checkpoint inhibitor)	• The anti-PD-1 antibody pembrolizumab prolonged progression-free survival and compared to ipilimumab in patients with advanced melanoma.
Nivolumab	1 preferred	Yes	Phase 3 (CheckMate-066), multi-center, double-blind, randomized trial 3-year follow-up	Dacarbazine	OS	Previously untreated	• Nivolumab improved response rates, PFS, and OS compared with chemotherapy in patients with previously untreated melanoma.
Nivolumab + ipilimumab, then nivolumab vs. nivolumab	1 preferred	Yes	Phase 3 (CheckMate-067), multicenter, randomized trial OS results	Ipilimumab	PFS OS	Previously untreated	• Among previously untreated patients with metastatic melanoma, nivolumab alone or combined with ipilimumab resulted in significantly longer PFS and OS than ipilimumab alone.
Subsequent therapy for unresectable or metastatic disease							

Regimen	NCCN Category	FDA Approved	Trial Design	Comparator	Primary End-Point	Line of Therapy	Conclusion
Pembrolizumab (2 mg/kg every 3 weeks or 10 mg/kg every 3 weeks)	2A preferred	Yes	Phase 2 (KEYNOTE-002), multi-center, randomized, active-controlled trial Final Analysis	Investigator's choice (paclitaxel/ carboplatin, paclitaxel, carboplatin, dacarbazine, oral temozolomide)	PFS	Second-line or subsequent therapy after ipilimumab and if BRAFV600 mutant-positive, a BRAF and/or MEK inhibitor	• Long-term follow-up showed that compared with chemotherapy, pembrolizumab provided higher rates and durations of response, and was associated with long-lasting improvements in PFS. The trend toward improved OS was not statistically significant.
Pembrolizumab + ipilimumab	2A preferred for progression after prior anti-PD-1 therapy	No	Phase 2	N/A	ORR	Subsequent therapy immediately after progression on prior single agent or combination anti-PD-1 therapy	• Combination therapy with low-dose ipilimumab with pembrolizumab demonstrated significant antitumor activity in patients with melanoma following disease progression on a PD1 antibody.
Ipilimumab (± gp100 vaccine)	2A other 2B (in combination with talimogene laherparepvec)	Yes	Phase 3 (CA184-002), randomized, double-blind, double-dummy	Gp100 vaccine	OS	Second-line or subsequent therapy. Patients with progression after showing initial clinical benefit (PR, CR, or stable disease ≥ 3 months duration after week 12) were eligible for reinduction therapy.	• Ipilimumab, with or without a gp100 peptide vaccine, as compared with gp100 alone, improved overall survival in patients with previously treated metastatic melanoma. Adverse events can be severe, long-lasting, or both, but most are reversible with appropriate treatment.
Nivolumab	2A preferred	Yes	Phase 3 (CheckMate 037), randomized,	Investigator's choice chemotherapy (dacarbazine,	ORR OS	Second-line or subsequent therapy after ipilimumab and if BRAFV600	• Nivolumab demonstrated higher, more durable responses but no

			controlled, open-label	carboplatin/ paclitaxel)		mutant-positive, a BRAF inhibitor	difference in survival compared with chemotherapy.
Nab-paclitaxel	2A certain circumstances	No	Phase 2	N/A	----------	Previously-treated and chemotherapy naive	• Nab-paclitaxel demonstrated activity in both previously treated and chemotherapy-naive patients with metastatic melanoma with ORR of 2.7% and 21.6%, respectively.
Nab-paclitaxel + carboplatin	2A certain circumstances	No	Phase 2, parallel study	N/A	ORR	Previously-treated and chemotherapy naive	• Nab-paclitaxel plus carboplatin demonstrated clinical activity in both chemo-naïve and previously treated patients (ORR 25.6% and 8.8%, respectively)
Paclitaxel + carboplatin + placebo	2A certain circumstances	No	Phase 3, randomized	Paclitaxel + carboplatin + sorafenib	PFS	Second-line (after dacarbazine or temozolomide-regimen)	• Addition of sorafenib to paclitaxel + carboplatin did not improve PFS or ORR in this second-line patient population
Paclitaxel + carboplatin	2A certain circumstances	No	Retrospective analysis	N/A	----------	Second-line	• Paclitaxel + carboplatin demonstrated clinical activity 26% partial responses and 19% having stable disease
Temozolomide	2A certain circumstances	No	Phase 3	Dacarbazine (DTIC)	----------	----------	• Temozolomide demonstrates efficacy equal to that of DTIC and is an oral alternative for patients with advanced metastatic melanoma
Paclitaxel (with premedication)	2A certain circumstances	No	Phase 2	N/A	----------	----------	• Taxol has activity in melanoma with an ORR of 14%
Nivolumab + ipilimumab	2A preferred	No	No clinical literature to support use.				
Dacarbazine	2A certain circumstances	Yes	See temozolomide above				

Retreatment of disease as re-induction							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Ipilimumab (± gp100 vaccine)	2A 2B (in combination with talimogene laherparepvec)	Yes	Phase 3 (CA184-002), randomized, double-blind, double-dummy	Gp100 vaccine	OS	Second-line or subsequent therapy. Patients with progression after showing initial clinical benefit (PR, CR, or stable disease ≥ 3 months duration after week 12) were eligible for reinduction therapy.	• Ipilimumab, with or without a gp100 peptide vaccine, as compared with gp100 alone, improved overall survival in patients with previously treated metastatic melanoma. Adverse events can be severe, long-lasting, or both, but most are reversible with appropriate treatment.
Pembrolizumab (10 mg/kg every 2 weeks or 10 mg/kg every 3 weeks)	1 preferred	Yes	Phase 3 (KEYNOTE-006), randomized, open-label, multi-center, active-controlled trial KEYNOTE-006 post-hoc 5-year results	Ipilimumab (4 doses unless discontinued earlier for disease progression or unacceptable toxicity)	PFS OS	First- or second-line therapy (no prior checkpoint inhibitor). Reinduction therapy also allowed.	• The anti-PD-1 antibody pembrolizumab prolonged progression-free survival and compared to ipilimumab in patients with advanced melanoma.
Nivolumab	2A	No	No clinical evidence to support use.				
Adjuvant treatment							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pembrolizumab	1 preferred (resected stage IIIA disease	Yes (with involvement of lymph	Phase 3 (KEYNOTE-054),	Placebo	RFS	Adjuvant therapy for completely	• At a median follow-up of 1.2 years, pembrolizumab improved RFS and reduced risk of distant metastases; OS

	with SLN metastases > 1mm, stage IIIB/C disease during nodal basin ultrasound surveillance or after CLND, stage III disease following wide excision or primary tumor and TLND, following TLDN and/or complete resection of nodal recurrence) 2A 2B (if NED after initial treatment with local or regional therapy)	node(s) following complete resection)	double-blind, randomized			resected stage III disease	data were not mature at the time of the initial report.
Ipilimumab (10 mg/kg every 3 weeks for 4 doses, then every 3 months for up to 3 years or disease	2A 2B (if NED after initial treatment with local or regional therapy)	Yes (pathologic involvement of regional lymph nodes of more than 1 mm who have	Phase 3 (EORTC 18071), double-blind, randomized	Placebo	RFS	Adjuvant therapy for completely resected stage III disease	• As adjuvant therapy for high-risk stage III melanoma, ipilimumab at a dose of 10 mg per kilogram resulted in significantly higher rates of recurrence-free survival, overall survival, and distant metastasis-free survival than placebo. There were

recurrence or unacceptable toxicities)		undergone complete resection, including total lymphadenec-tomy)					more immune-related adverse events with ipilimumab than with placebo.
Nivolumab + placebo	1 preferred (resected stage IIIA disease with SLN metastases > 1mm, stage IIIB/C disease during nodal basin ultrasound surveillance or after CLND, stage III disease following wide excision or primary tumor and TLND, following TLDN and/or complete resection of nodal recurrence) 2A 2B (if NED after initial treatment with	Yes (with involvement of lymph nodes or metastatic disease who have undergone complete resection)	Phase 3 (CheckMate 238), double-blind, randomized	Ipilimumab + placebo	RFS	Adjuvant therapy for completely resected stage IIIB/C or stage IV disease	• At a median 19.5 months follow-up, nivolumab was associated with a clinically meaningful and statistically significant improvement in RFS and DMFS. The percent of patients experiencing grade 3-4 AEs was 30% lower in the nivolumab versus ipilimumab arm.

	local or regional therapy)						

Uveal Melanoma

Distant metastatic disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pembrolizumab	2A	No	Case report (10 patients)	N/A	N/A	Subsequent therapy after prior ipilimumab	• Pembrolizumab demonstrated a PFS of 18 weeks in patients with metastatic uveal melanoma. Out of 8 evaluable patients, there were 1 complete response, 2 partial response, and 1 patient with stable disease.
PD-1 and PD-L1 antibodies (pembrolizumab, nivolumab, atezolizumab)	2A	No	Multicenter retrospective series	N/A	N/A	Not specified	• Responses and clinical benefit with pembrolizumab or nivolumab are more limited than with advanced cutaneous melanoma. Out of 56 patients, there were 1 partial response and 5 patients with stable disease.
Nivolumab + ipilimumab	2A	No	Phase 2 (GEM 1402, open label)	N/A	OS	Previously untreated	• Combination of NIVO+IPI is feasible in terms of efficacy for first-line treatment of metastatic uveal melanoma with a disease stabilization rate of 52% and disease control rate of 64%.
Ipilimumab	2A	No	Phase 2 (DeCOG-study)	N/A	OS	Pretreated and treatment-naïve	• Ipilimumab has limited clinical activity in patients with metastatic uveal melanoma. Sixteen out of 53 patients had stable disease (47%), but none experienced a partial or complete response.
Ipilimumab	2A	No	Phase 2 (GEM-1), open label	N/A	Not specified	Previously untreated	• Ipilimumab demonstrated to have limited clinical activity in the first-line treatment of metastatic uveal melanoma with 7.7% having a partial response and 46.2% having stable disease.

Ipilimumab	2A	No	Retrospective analysis	N/A	N/A	Not specified	• Retrospective analysis of patients with uveal melanoma at 4 hospitals in the United States and Europe demonstrated a stable disease rate of 26.2% at 23 weeks.
Trametinib	2A	No	Phase 2, randomized, open label	Trametinib + GSK2141795 (GSK795)	Not specified	Previously untreated	• The addition of GSK795 to trametinib did not improve PFS and only 1 partial response were seen in both treatment arms.
Temozolomide	2A	No	Phase 2	N/A	Not specified	Not specified	• Temozolomide is not effective for the control of metastatic melanoma of uveal origin
Nab-paclitaxel	2A	No	Clinical literature is for the treatment of cutaneous melanoma. No clinical trial data specific for uveal melanoma.				
Dacarbazine	2A	No	Clinical literature is for the treatment of cutaneous melanoma. No clinical trial data specific for uveal melanoma.				
Paclitaxel + carboplatin	2A	No	Clinical literature is for the treatment of cutaneous melanoma. No clinical trial data specific for uveal melanoma.				
Paclitaxel (with premedication)	2A	No	Clinical literature is for the treatment of cutaneous melanoma. No clinical trial data specific for uveal melanoma.				

Gastric Cancer

First-line therapy for HER2-postiive disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pembrolizumab + 5-FU + cisplatin + trastuzumab Pembrolizumab + capecitabine + oxaliplatin + trastuzumab	TBD	Yes	KEYNOTE-811, randomized, double-blind, placebo-controlled	Placebo + chemotherapy + trastuzumab	PFS OS	Previously untreated, locally advanced unresectable or metastatic HER2 positive gastric or GEJ adenocarcinoma	• Pembrolizumab in combination with a fluoropyrimidine, platinum, and trastuzumab demonstrated a statistically significant improvement in ORR compared to chemotherapy plus trastuzumab alone in first-line treatment of patients with locally advanced unresectable or metastatic HER2-positive

							gastric or gastroesophageal junction adenocarcinoma.
Subsequent therapy for PD-L1-positive recurrent or metastatic disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pembrolizumab	2A preferred	Yes	Phase 2 (KEYOTE-059), single-arm, multi-cohort trial	N/A	ORR	Third-line or later therapy (including a fluoropyrimidine and a platinum doublet; if HER2-positive, must have previously received trastuzumab)	• Pembrolizumab monotherapy demonstrated an ORR of 15.5% and a median duration of response of 16.3 months in patients with PD-L1-positive advanced gastric or gastroesophageal junction cancer who had previously received at least 2 lines of treatment.

Esophageal or Gastroesophageal Junction Cancer

First-line therapy for PD-L1-positive recurrent or metastatic disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pembrolizumab + fluorouracil or capecitabine + cisplatin or oxaliplatin	1 preferred CPS ≥10 with cisplatin 2A preferred CPS ≥10 with oxaliplatin	Yes	Phase 3 (KEYNOTE-590), randomized, double-blind, placebo-controlled	Placebo + fluorouracil + cisplatin	OS PFS	First-line	• First-line pembrolizumab plus chemotherapy demonstrated superior OS, PFS, and ORR compared to chemotherapy alone in patients with untreated advanced esophageal and EGJ cancer.
Nivolumab + (fluorouracil or capecitabine) + oxaliplatin	1 preferred PD-L1 CPS ≥5 (adenocarcinoma only)	No	Phase 3 (CheckMate 649), randomized, multi-center, open-label	XELOX (capecitabine + oxaliplatin) or FOLFOX	OS PFS	First-line	• Nivolumab plus chemotherapy prolonged PFS and OS compared with chemotherapy alone in first-line treatment of gastric, gastroesophageal junction, and esophageal cancers with PD-L1 CPS ≥5. OS was improved with nivolumab plus chemotherapy in all randomized patients.

Subsequent therapy for PD-L1-positive recurrent or metastatic disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pembrolizumab	1 preferred (second-line therapy for esophageal SCC with PD-L1 CPS ≥10) 2A preferred (third-line or subsequent therapy for PD-L1 CPS ≥1)	Yes (ESCC CPS ≥10 and GEJ adenocarcinoma CPS ≥1)	Phase 3 (KEYNOTE-181), multicenter, randomized, open-label, active-controlled trial	Investigator's Choice (paclitaxel, docetaxel, irinotecan)	OS	Second-line therapy (if HER2-positive, must have previously received HER2-targeted therapy)	• Data from KEYNOTE-181 suggest that pembrolizumab may be an effective second-line therapy for patients with advanced esophageal cancer with a PD-L1 CPS ≥10, with a more favorable safety profile than chemotherapy.
Pembrolizumab	1 preferred (second-line therapy for esophageal SCC with PD-L1 CPS ≥10) 2A preferred (third-line or subsequent therapy for PD-L1 CPS ≥1)	Yes (ESCC CPS ≥10 and GEJ adenocarcinoma CPS ≥1)	Phase 2 (KEYOTE-059), single-arm, multi-cohort trial	N/A	ORR	Third-line or later therapy (if HER2-positive, must have previously received trastuzumab)	• Pembrolizumab monotherapy demonstrated an ORR of 15.5% and a median duration of response of 16.3 months in patients with PD-L1-positive advanced gastric or gastroesophageal junction cancer who had previously received at least 2 lines of treatment.
Nivolumab	1 preferred	Yes	Phase 3 (ATTRACTION-3), multi-center, randomized, open-label	Paclitaxel or docetaxel	OS	After prior fluoropyrimidine-based and platinum-based chemotherapy	• Nivolumab was associated with a significant improvement in overall survival and a favorable safety profile compared with chemotherapy in previously treated patients with advanced oesophageal squamous cell carcinoma,

Merkel Cell Carcinoma

Locally advanced or metastatic disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pembrolizumab	2A preferred	Yes	Phase 2 (KEYNOTE-017), multi-center, open-label	N/A	ORR	First-line therapy	• First-line therapy with pembrolizumab in patients with advanced Merkel-cell carcinoma was associated with an objective response rate of 56%.
Avelumab	2A preferred	Yes	Phase 2 (JAVELIN Merkel 200, part B), multicenter, international, single-arm, open-label	N/A	ORR	First-line for distant metastatic disease	• First-line avelumab monotherapy in patients with mMCC was associated with high response rates and a manageable safety profile
Avelumab	2A preferred	Yes	Phase 2 (JAVELIN Merkel 200, part A), multicenter, international, single-arm, open-label	N/A	ORR	Second-line or later for distant metastatic disease	• Avelumab demonstrated durable responses and promising survival outcomes in patients with mMCC whose disease had progressed after chemotherapy
Nivolumab	2A preferred	No	Phase 1/2 (Checkmate 358)	N/A	ORR	First- to third-line	• Nivolumab induced durable tumor regression with an ORR of 68%.

Non-Small Cell Lung Cancer (NSCLC)

Stage III disease – PD-L1 ≥1%, EGFR/ALK negative							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pembrolizumab	1 preferred (PD-L1 ≥50%)	Yes (stage III NSCLC, who are not	Phase 3 (KEYNOTE-042),	Investigator's Choice (pemetrexed	OS	First-line	• The trial demonstrated a statistically significant improvement in OS for

	2B (PD-L1 1%-49%)	candidates for surgical resection or definitive chemoradiation, or metastatic NSCLC whose tumors have high PD-L1 expression ≥1%] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations)	randomized, multicenter, open-label, active-controlled trial	+ carboplatin followed by optional pemetrexed, paclitaxel + carboplatin followed by optional pemetrexed)			patients (PD-L1 TPS ≥50%, TPS ≥20%, TPS ≥1%) randomized to pembrolizumab as compared with chemotherapy. • Exploratory analysis showed little survival advantage with pembrolizumab versus chemotherapy in patients with a TPS 1% to 49%.
First-line therapy for recurrent, advanced, or metastatic disease – Squamous cell histology							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Nab-paclitaxel (or paclitaxel) + pembrolizumab + carboplatin, followed by pembrolizumab for up to 35 cycles total	1 preferred (EGFR, ALK, ROS1, BRAF negative; regardless of PD-L1 expression; useful under certain circumstances for BRAF V600E-mutation positive or NTRK gene	Yes	Phase 3 (KEYNOTE-407), double-blind, randomized (1:1)	Nab-paclitaxel (or paclitaxel) + carboplatin + placebo, followed by placebo for up to 35 cycles total	OS PFS	First-line	• In patients with previously untreated metastatic, squamous NSCLC, the addition of pembrolizumab to chemotherapy with carboplatin plus paclitaxel or nab-paclitaxel resulted in significantly longer overall survival and progression-free survival than chemotherapy alone regardless of PD-L1 expression. • No difference between paclitaxel of nab-paclitaxel was observed

	fusion positive tumors)						
Pembrolizumab	1 preferred (if PD-L1 ≥50%) 2B (if PD-L1 1%-49%)	Yes	Phase 3 (KEYNOTE-024), open-label, randomized	Platinum-based chemotherapy	PFS	First-line	• In patients with advanced NSCLC and PD-L1 expression on at least 50% of tumor cells, pembrolizumab was associated with significantly longer progression-free and overall survival and with fewer adverse events than was platinum-based chemotherapy
Atezolizumab	1 preferred for PD-L1 ≥50%	Yes for TC ≥50% or IC ≥10%	Phase 3 (IMpower110), randomized, open-label	Carboplatin or cisplatin + pemetrexed (non-squamous) or gemcitabine (squamous)	OS	First-line	• IMpower110 met the primary OS endpoint with statistically significant and clinically meaningful improvement as first-line therapy in patients with TC ≥50% or IC ≥10%.
Cemiplimab-rwlc	1 preferred for PD-L1 ≥50%	Yes for TPS ≥50%	Phase 3 (EMPOWER-Lung 1), randomized, multi-center, open-label, controlled	Platinum-doublet chemotherapy	OS PFS	First-line	• Cemiplimab monotherapy significantly improved overall survival and progression-free survival compared with chemotherapy in patients with advanced non-small-cell lung cancer with PD-L1 of at least 50%.
Dabrafenib + trametinib	2A preferred	Yes (in combination with trametinib for BRAF V600E mutation-positive metastatic NSCLC)	Cohort C of Phase 2 (Study BRF113928), multi-center, open-label	N/A	ORR	First-line	• Dabrafenib plus trametinib demonstrated a clinically meaningful antitumor activity with an ORR of 64% and a manageable safety profile in patients with previously untreated BRAFV600E-mutant NSCLC.
Dabrafenib	2A	No	Cohort A of Phase 2 (Study BRF113928),	N/A	ORR	Previously untreated and	• In previously untreated patients with BRAF V600E-positive NSCLC, 4 out of

			multi-center, open-label			treated patients	6 patients achieved an objective response.
BRAF therapy (vemurafenib, dabrafenib, sorafenib)	2A	No	Retrospective multicenter cohort study	N/A	------	All lines of therapy	• Targeted therapy in patients with BRAF-mutant lung adenocarcinoma demonstrated an ORR of 53% and DCR of 85%.
Larotrectinib	2A preferred	Yes (for NTRK gene fusion positive tumors)	Phase 1/2 (Study LOXO-TRK-14001, SCOUT, and NAVIGATE)	N/A	ORR	All lines of therapy (98% had received prior treatment)	• Larotrectinib demonstrated an ORR of 75% in patents with NTRK gene fusion positive disease across a range of solid tumors.
Entrectinib	2A preferred	Yes	Phase 1/2 (STARTRK-2, STARTRK-1 and ALKA-372-001)	N/A	ORR DOR	TRK inhibitor-naïve	• Entrectinib induced clinically meaningful responses in patients with NTRK-FP solid tumors, including those with NSCLC (ORR 70%).
Nivolumab	2A	No	Phase 3 (CheckMate-026), randomized, open-label	Investigator's choice [non-squamous: gemcitabine/ cisplatin (or carboplatin), paclitaxel/ carboplatin; squamous: pemetrexed/ carboplatin (or cisplatin)]	PFS	Previously untreated	• In an exploratory, hypothesis-generating analysis, among patients with a high tumor-mutation burden, nivolumab was associated with a higher response rate than chemotherapy (47% vs. 28%) and with a longer median progression-free survival (9.7 vs. 5.8 months).
Nivolumab + ipilimumab	2A	No	Phase 3, (CheckMate-227), randomized, open-label	Platinum-doublet chemotherapy	OS PFS	Previously untreated	• Progression-free survival was significantly longer with first-line nivolumab plus ipilimumab than with chemotherapy among patients with NSCLC and a high tumor mutational

							burden, irrespective of PD-L1 expression level.
Capmatinib	2A preferred	Yes	Phase 2 (GEOMETRY mono-1)	N/A	ORR	≤2 prior lines of therapy	• Capmatinib showed substantial antitumor activity in patients with advanced NSCLC with a MET exon 14 skipping mutation, particularly in those not treated previously (ORR 68%).
Tepotinib	2A preferred	Yes	Phase 2 (VISION), open-label	N/A	ORR	All lines of therapy	• Among patients with advanced NSCLC with a confirmed MET exon 14 skipping mutation, the use of tepotinib was associated with an ORR of 46%.
First-line therapy for recurrent, advanced, or metastatic disease – Non-squamous cell histology							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pembrolizumab + carboplatin (or cisplatin) + pemetrexed, followed by pembrolizumab + pemetrexed for up to 35 cycles total	1 preferred (for adeno-carcinoma only; EGFR, ALK, ROS1, BRAF negative; regardless of PD-L1 expression) 2A useful under certain circumstances (BRAF V600E-mutation positive or NTRK gene	Yes	Phase 3 (KEYNOTE-189), double-blind, randomized (2:1)	Carboplatin (or cisplatin) + pemetrexed + placebo, followed by placebo + pemetrexed for up to 35 cycles total	OS PFS	First-line	• In patients with previously untreated metastatic nonsquamous NSCLC without EGFR or ALK mutations, the addition of pembrolizumab to standard chemotherapy of pemetrexed and a platinum-based drug resulted in significantly longer overall survival and progression-free survival than chemotherapy alone

	fusion positive tumors)						
Pembrolizumab	1 preferred (if PD-L1 ≥50%) 2B (if PD-L1 1%-49%)	Yes	Phase 3 (KEYNOTE-024), open-label, randomized	Platinum-based chemotherapy	PFS	First-line	• In patients with advanced NSCLC and PD-L1 expression on at least 50% of tumor cells, pembrolizumab was associated with significantly longer progression-free and overall survival and with fewer adverse events than was platinum-based chemotherapy
Atezolizumab	1 preferred for PD-L1 ≥50%	Yes for TC ≥50% or IC ≥10%	Phase 3 (IMpower110), randomized, open-label	Carboplatin or cisplatin + pemetrexed (non-squamous) or gemcitabine (squamous)	OS	First-line	• IMpower110 met the primary OS endpoint with statistically significant and clinically meaningful improvement as first-line therapy in patients with TC ≥50% or IC ≥10%.
Cemiplimab-rwlc	1 preferred for PD-L1 ≥50%	Yes for TPS ≥50%	Phase 3 (EMPOWER-Lung 1), randomized, multi-center, open-label, controlled	Platinum-doublet chemotherapy	OS PFS	First-line	• Cemiplimab monotherapy significantly improved overall survival and progression-free survival compared with chemotherapy in patients with advanced non-small-cell lung cancer with PD-L1 of at least 50%.
Subsequent therapy for recurrent, advanced, or metastatic disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pembrolizumab (2 mg/kg vs. 10 mg/kg)	1 preferred (first progression)	Yes (PD-L1 ≥1% with disease progression on or after platinum-containing chemotherapy.	Phase 2/3 (KEYNOTE-010), randomized, multicenter, open-label,	Docetaxel	OS PFS	Previously treated	• Pembrolizumab prolongs overall survival in patients with previously treated, PD-L1-positive, advanced non-small-cell lung cancer.

	2A (subsequent progression)	Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving pembrolizumab)	active-controlled trial				
Nivolumab	1 preferred (first progression) 2A (subsequent progression)	Yes (with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations)	Phase 3 (CheckMate-017), randomized, open-label	Docetaxel	OS	After one prior platinum doublet-based therapy	• Among patients with advanced, previously treated squamous-cell NSCLC, overall survival, response rate, and progression-free survival were significantly better with nivolumab than with docetaxel, regardless of PD-L1 expression level.
Nivolumab	1 (for first progression) 2A (for subsequent progression)	Yes	Phase 3 (CheckMate 057), randomized, open-label	Docetaxel	OS	Subsequent	• Among patients with advanced nonsquamous NSCLC that had progressed during or after platinum-based chemotherapy, overall survival was longer with nivolumab than with docetaxel
Atezolizumab	1 (for first progression)	Yes (after platinum therapy)	Phase 3 (OAK), open-label,	Docetaxel	OS	Second- or third-line	• Atezolizumab treatment results in a statistically significant and clinically

	2A (for subsequent progression)		multicenter randomized (1:1)				relevant improvement in OS versus docetaxel in second- and third-line NSCLC, regardless of PD-L1 expression and histology
Osimertinib	1 preferred (T790M+)	Yes for EGFR T790M+ NSCLC that has progressed on EGFR TKI therapy	Phase 3 (AURA3), randomized, open-label	Pemetrexed + carboplatin or cisplatin	PFS	After first-line EGFR-TKI therapy	• Osimertinib had significantly greater efficacy than platinum therapy plus pemetrexed in patients with T790M-positive advanced non-small-cell lung cancer (including those with CNS metastases) in whom disease had progressed during first-line EGFR-TKI therapy. PFS and ORR was significantly better with osimertinib compared to platinum therapy plus pemetrexed.
Lorlatinib	2A (ALK- or ROS1-positive)	Yes for ALK-positive NSCLC after progression on crizotinib and at least one other ALK inhibitor for metastatic disease or after first-line alectinib or ceritinib	Phase 2	N/A	ORR	Previously treated with ≥1 ALK inhibitor	• Lorlatinib demonstrated an ORR of 47% in patients with ALK-positive metastatic NSCLC previously treated with ≥1 ALK inhibitor.
Alectinib	2A (ALK-positive, after progression on crizotinib)	Yes for ALK-positive mNSCLC	Phase 2	N/A	ORR	Crizotinib-refractory	• Alectinib is highly active and well tolerated in patients with advanced, crizotinib-refractory ALK-positive NSCLC with an ORR of 50%.
Brigatinib (90 mg vs. 180 mg daily)	2A (ALK-positive, after progression on crizotinib)	Yes for ALK-positive mNSCLC that has progressed on or intolerant to crizotinib	Phase 2 (ALTA), randomized	N/A	ORR	Crizotinib-refractory	• Brigatinib (180 mg once daily with lead-in) demonstrated a longer PFS and ORR 56% in patients with crizotinib refractory ALK-positive NSCLC.

Ceritinib	2A (ALK-positive, after progression on crizotinib)	Yes for ALK-positive mNSCLC	Phase 3 (ASCEND-5), randomized, controlled, open-label	Pemetrexed or docetaxel	PFS	Progressed following crizotinib and platinum-based doublet chemotherapy	• After failure of crizotinib, ceritinib significantly improved PFS compared to single-agent chemotherapy

Chapter 1 Squamous Cell Carcinoma of the Head and Neck (SCCHN)

First-line therapy

Regimen	NCCN Category	FDA Approved	Trial Design	Comparator	Primary End-Point	Line of Therapy	Conclusion
Pembrolizumab ± carboplatin (or cisplatin) + 5-FU	2A preferred	Yes	Phase 3 (KEYNOTE-048), randomized, open-label	EXTREME regimen [cetuximab + carboplatin (or cisplatin) + 5-FU]	OS PFS	First-line	• The addition of pembrolizumab to a platinum and fluorouracil combination improved overall survival compared with cetuximab plus a platinum and fluorouracil combination. For those with high PD-L1 expression (CPS ≥1), single-agent pembrolizumab also improved overall survival compared with cetuximab plus a platinum and fluorouracil combination.
Cetuximab + cisplatin (or carboplatin) + fluorouracil, followed by maintenance cetuximab	1 preferred	Yes	Phase 3 (EXTREME), randomized	Cisplatin (or carboplatin) + fluorouracil	OS	First-line therapy	• As compared with platinum-based chemotherapy plus fluorouracil alone, cetuximab plus platinum-fluorouracil chemotherapy improved overall survival when given as first-line treatment in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck.

Subsequent therapy

Regimen	NCCN Category	FDA Approved	Trial Design	Comparator	Primary End-Point	Line of Therapy	Conclusion
Pembrolizumab	1 preferred	Yes	Phase 3 (KEYNOTE-040),	Investigator's choice (methotrexate,	OS	After platinum-based	• Pembrolizumab improved OS compared to the standard of care arm (methotrexate, docetaxel, or cetuximab)

			randomized, open-label PD-L1 results	docetaxel, cetuximab)		chemo for recurrent or metastatic disease	however, improvement was only marginal and the study did not reach its primary endpoint of OS. However, when analysis was stratified by PD-L1 status, results for OS in patients with positive PD-L1 expression was statistically significant.
Pembrolizumab (200mg every 3 weeks)	1 preferred	Yes	Phase 1b (KEYNOTE-012) expansion cohort	N/A	ORR	After disease progression on or after platinum-containing therapy	• A lower, fixed dose schedule using pembrolizumab 200 mg every 3 weeks demonstrated an ORR of 18% and a 6-month OS rate of 59%.
Nivolumab	1 preferred	Yes	Phase 3 (CheckMate-141), randomized, open-label	Investigator's choice (methotrexate, docetaxel, cetuximab)	OS	After platinum-based chemo for recurrent or metastatic disease	• Among patients with platinum-refractory, recurrent squamous-cell carcinoma of the head and neck, treatment with nivolumab resulted in longer overall survival than treatment with standard, single-agent therapy. No OS advantage was demonstrated for the nivolumab-treated patients with PD-L1 expression less than 1%.
Pembrolizumab ± carboplatin (or cisplatin) + 5-FU	2A	No	No clinical literature evidence to support use.				

Classic Hodgkin Lymphoma (cHL)

Relapsed or refractory disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pembrolizumab	2A	Yes (pediatric and adults)	Phase 2 (KEYNOTE-087)	N/A	ORR	After ASCT with or without brentuximab vedotin or after salvage	• Among heavily pretreated patients with relapsed or refractory cHL who received pembrolizumab, median PFS was 14 months;

			2-year follow-up			chemotherapy and brentuximab vedotin (chemo-resistant disease and ineligible for ASCT)	for patients who achieved a complete response, two-year PFS was >60 percent.
Pembrolizumab	2A	Yes	Phase 1b (KEYNOTE-013)	N/A	ORR AEs	Relapsed or refractory disease after brentuximab vedotin	• Pembrolizumab was associated with a favorable safety profile and induced favorable responses (ORR 65%) in a heavily pretreated patient cohort.
Pembrolizumab	2A	Yes	Phase 3 (KEYNOTE-204), randomized, open-label	Brentuximab vedotin (BV)	OS PFS	Relapsed or refractory cHL after at least one multi-agent chemotherapy regimen	• In the phase III KEYNOTE-204 trial, pembrolizumab significantly improved progression-free survival compared with brentuximab vedotin in patients with relapsed or refractory classic Hodgkin lymphoma.
Pembrolizumab	2A	Yes	Phase 1/2 (KEYNOTE-051), open-label, single-arm	N/A	ORR	Relapsed or refractory cHL	• Pembrolizumab was well tolerated and showed an ORR 60% in pediatric patients with relapsed or refractory Hodgkin lymphoma, consistent with experience in adult patients.
Nivolumab	2A (subsequent therapy)	Yes (after ASCT and brentuximab vedotin or 3 or more lines of systemic therapy that includes ASCT)	Phase 2 (CheckMate-205) Extended-follow up	N/A	ORR	Relapsed or refractory disease after HDT/ASCR with or without brentuximab vedotin	• Nivolumab demonstrated a response rate of 66.3% and an acceptable safety profile in patients with cHL who progressed following autologous stem-cell transplantation and brentuximab vedotin. Extended follow-up resulted an overall ORR of 69% after ASCT with or without brentuximab vedotin.
Brentuximab vedotin	2A (second-line and later therapy)	Yes (after failure of HDT/ASCR or at least 2 prior chemo	Phase 2	N/A	ORR	Relapsed or refractory CD30-positive disease after HDT/ASCR	• Brentuximab vedotin induced an ORR of 75% in patients with relapsed or refractory HL after auto-SCT.

		regimens in patients not candidates for HDT/ASCR)	3-year follow-up				
Brentuximab vedotin (BV)	2A (second-line and later therapy)	Yes (after failure of HDT/ASCR or at least 2 prior chemo regimens in patients not candidates for HDT/ASCR)	Phase 2	N/A	ORR	First line salvage therapy in relapsed/refractory HL prior to ASCT	• BV as first line salvage therapy is efficacious, well tolerated, and does not hinder stem cell collection or engraftment. 90% of patients were effectively bridged to ASCT and 52% did not require multi-agent chemotherapy.
Bendamustine	2A (subsequent)	No	Phase 2	N/A	ORR	Relapsed or refractory disease (including failure to HDT/ASCR)	• This study confirms the efficacy of bendamustine in heavily pretreated patients with HL (ORR 53%).
Gemcitabine + carboplatin + dexamethasone (GCD) (+ rituximab)	2A (subsequent therapy)	No	Phase 2, multi-center	N/A	ORR	Relapsed or refractory disease	• GCD(R) is a safe and effective regimen for relapsed lymphoma with an overall ORR of 67%.
Etoposide + ifosfamide + mesna + mitoxantrone (MINE)	2A (subsequent therapy)	No	Phase 2	N/A	-----	Refractory disease after prior cytarabine/ platinum treatment	• The MINE regimen induced responses in a moderate fraction of patients after their prior exposure to cytarabine/ platinum salvage therapy
Carmustine + cytarabine + etoposide + melphalan (Mini-BEAM)	2A (subsequent therapy)	No	Clinical trial	N/A	-----	Relapsed or refractory HL	• Mini-BEAM is a safe and effective regimen for treatment of refractory or relapsed Hodgkin's disease with an ORR of 84%

Carmustine + cytarabine + etoposide + melphalan (Mini-BEAM)	2A (subsequent therapy)	No	Long-term study	N/A	-----	Relapsed or refractory HL	• Results showed an ORR of 84% with Mini-BEAM before ASCT for refractory or relapsed HD patients.

Primary Mediastinal Large B-Cell Lymphoma (PMBCL)

Relapsed or refractory disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pembrolizumab	2A	Yes	Phase 2 (KEYNOTE-170)	N/A	ORR	Relapsed after ASCT or if ineligible for ASCT, after ≥2 prior lines of therapy	• Pembrolizumab achieved responses in 45% of patients with relapsed or refractory PMBCL.
Pembrolizumab	2A	Yes	Phase 1b, (KEYNOTE-103), multi-cohort trial	N/A	ORR AE	Relapsed or refractory disease	• PD-1 blockade with pembrolizumab demonstrated an ORR 41% after a median follow-up of 11 months.

Bladder Cancer/Urothelial Carcinoma

Bacillus Calmette-Guerin (BCG)-unresponsive, non-muscle invasive bladder cancer (NMIBC)							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pembrolizumab	2A	Yes	Phase 2 (KEYNOTE-057)	N/A	CR	BCG-unresponsive carcinoma in situ (CIS), with or without papillary disease, who received adequate BCG therapy and were unable/unwilling to	• Pembrolizumab demonstrated a 3-month complete response rate of 38.5% with 72.5% of patients maintaining CR at last follow-up.

						undergo radical cystectomy	
First-line therapy in cisplatin-ineligible patients expressing PD-L1 [Combined Positive Score (CPS) ≥10] or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pembrolizumab	2A	Yes	Phase 2 (KEYNOTE-052), open-label	N/A	ORR	First-line	• Results from the KEYNOTE-052 study showed pembrolizumab elicits an ORR of 27% and durable responses with a 6-month OS rate of 67% in cisplatin-ineligible patients with urothelial carcinoma.
Pembrolizumab	2A	Yes	Phase 3 (KEYNOTE-361) *Ongoing*	Gemcitabine + cisplatin (or carboplatin)	PFS OS	First-line	• Pembrolizumab monotherapy had decreased survival compared to patients receiving platinum-based chemotherapy in patients with metastatic urothelial cancer who have not received prior therapy and who have low PD-L1 expression.
Atezolizumab	2A preferred	Yes	Phase 2 (IMvigor210 – Cohort 1), single-arm, multi-center	N/A	ORR	First-line	• Atezolizumab was associated with an overall ORR of 23% and with a median OS of 15.9 months.
							•
Gemcitabine + carboplatin	2A preferred	No	Phase 2/3 (EORTC Study 30986), randomized	Methotrexate + carboplatin + vinblastine (M-CAVI)	OS	Chemo-naïve Cisplatin-ineligible (GFR between 30-60mL/min and/or ECOG ≥2)	• There were no significant differences in efficacy between the two treatment groups. The incidence of severe acute toxicities was higher for those receiving M-CAVI.
Avelumab + best supportive care	1 preferred	Yes	Phase 3 (JAVELIN	Best supportive care (BSC)	OS	Patients without progression on platinum-	• First-line maintenance therapy with avelumab in patients with advanced urothelial cancer whose

			Bladder 100), randomized, multi-center, open-label			based induction chemotherapy (4-6 cycles of gemcitabine + cisplatin or carboplatin)	disease has not progressed with platinum-based induction chemotherapy demonstrated a significantly longer OS compared to best supportive care in both overall and PD-L1-positive populations.
Relapsed or refractory disease (platinum-refractory)							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pembrolizumab	1 (second-line therapy post-platinum) 2A (subsequent therapy)	Yes	Phase 3 (KEYNOTE-045), open-label, randomized	Investigator's choice: paclitaxel, docetaxel, or vinflunine	OS PFS	Second-line or later (platinum-refractory disease)	• Pembrolizumab was associated with significantly longer overall survival (by approximately 3 months) compared to chemotherapy.
Avelumab	2A alternative preferred	Yes	Phase 1b	N/A	Safety ORR (secondary end-point)	Second-line or later (platinum refractory, carcinoma of the renal pelvis, ureter, urinary bladder, or urethra)	• Avelumab was well tolerated and associated with an ORR of 18.2%
Avelumab	2A alternative preferred	Yes	Pooled analysis from 2 expansion cohorts of a Phase 1 trial (JAVELIN Solid Tumor)	N/A	ORR	Second-line or later (platinum refractory, general urothelial carcinoma) or within 12 months of platinum-containing neoadjuvant or adjuvant chemotherapy	• Avelumab showed antitumor activity in the treatment of patients with platinum-refractory metastatic urothelial carcinoma with an 6-month ORR of 17%.
Atezolizumab	2A alternative preferred	Yes	Phase 2 (IMvigor210 – Cohort 2),	N/A	ORR	Cohort 2: Second-line or later (platinum-refractory disease)	• Atezolizumab showed durable activity with an ORR of 15% and good tolerability. Increased levels of PD-L1 expression on

			single-arm, multicenter				immune cells were associated with increased response.
Atezolizumab	2A alternative preferred	Yes	Phase 3 (IMvigor211), randomized, controlled	Chemotherapy (vinflunine, paclitaxel, or docetaxel)	OS in patients with PD-L1 ≥5%	After platinum-therapy	• Atezolizumab was not associated with significantly longer overall survival than chemotherapy in patients with platinum-refractory metastatic urothelial carcinoma overexpressing PD-L1 (IC2/3). However, the safety profile for atezolizumab was favorable compared with chemotherapy.
Nivolumab	2A alternative preferred	Yes	Phase 2 (CheckMate 275), single-arm, multicenter	N/A	ORR	Second-line or later (platinum refractory)	• Nivolumab monotherapy demonstrated an ORR of 19.6%. Benefit was observed irrespective of PD-L1 expression.
Durvalumab	Not recommended	Yes	Phase 1/2 (MEDI4736), multicenter, open-label	N/A	ORR Safety	Any line of therapy	• The ORR was 31.0% in 42 response-evaluable patients. The response rate was higher in high PD-L1 expression tumors compared with low or negative PD-L1 expression.
Erdafitinib	2A alternative preferred (post-platinum, FGFR3 or FGFR2 genetic alterations)	Yes (for FGFR3 or FGFR2 genetic alterations)	Phase 2 (BLC2001), open-label	N/A	ORR	After ≥ 1 line of prior chemo or ≤ 12 mon of [neo]adjuvant chemo, or were cisplatin ineligible, chemo naïve	• Treatment with erdafitinib yielded an ORR of 42% and was tolerable in patients with chemo-refractory metastatic urothelial carcinoma and FGFR generic alterations.

Cervical Cancer

Second-line therapy

Regimen	NCCN Category	FDA Approved	Trial Design	Comparator	Primary End-Point	Line of Therapy	Conclusion
Pembrolizumab	2A preferred	Yes after chemotherapy whose tumors express PD-L1 (CPS ≥1)	Phase 2 (KEYNOTE-158), multi-cohort, randomized – Cohort E	N/A	ORR	Previously treated	• Pembrolizumab monotherapy demonstrated an ORR of 14.3% among patients with patients with advanced, pretreated cervical cancer and PD-L1 expression of 1 percent or more.

Microsatellite Instability-High (MSI-H) Cancer

Colorectal Cancer (CRC) – First-line therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pembrolizumab	2A preferred	Yes	Phase 3 (KEYNOTE-177), randomized, open-label	Standard of care chemotherapy (FOLFOX or FOLFIRI ± bevacizumab or cetuximab)	PFS OS	First-line	• Pembrolizumab demonstrated a clinically meaningful and statistically significant 40% reduction in the risk of disease progression compared to chemotherapy in patients with MSI-H or dMMR CRC.
Nivolumab + ipilimumab, followed by nivolumab	2B	No	Phase 2 (CheckMate-142) Follow-up data	N/A	ORR	First-line	• ORR was found to be 60% in patients with previously untreated MSI-H/dMMR metastatic CRC.
Nivolumab	2A	No	No clinical literature to support use.				
Colorectal Cancer (CRC) – Subsequent therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**

Pembrolizumab	2A preferred	Yes	Phase 2 (KEYNOTE-016)	N/A	ORR 20-week PFS	CRC: after at least 2 prior cancer therapy regimens Non-CRC: after at least 1 prior cancer therapy	• This study showed that mismatch-repair status predicted clinical benefit of immune checkpoint blockade with pembrolizumab (ORR 40% and 20-week PFs 78%).
Pembrolizumab	2A preferred	Yes	Phase 2 (KEYNOTE-164)	N/A	ORR	Cohort A: after prior fluoropyrimidine, oxaliplatin, and irinotecan Cohort B: after prior fluoropyrimidine + oxaliplatin or fluoropyrimidine + irinotecan +/- anti-VEGF/EGFR monoclonal antibody (mAb)	• Pembrolizumab demonstrated anti-tumor efficacy in patients with previously treated dMMR metastatic colorectal cancer with an ORR of 33%.
Nivolumab ± ipilimumab	2A	Yes	Phase 2 (CheckMate-142) Nivolumab + ipilimumab cohort	N/A	ORR	Progressed on or after, or been intolerant of, at least one previous line of treatment, including a fluoropyrimidine and oxaliplatin or irinotecan	• Nivolumab monotherapy and nivolumab in combination with ipilimumab demonstrated an ORR of 31.5% and 55%, respectively, in pre-treated patients with dMMR/MSI-H metastatic colorectal cancer.
Pancreatic Adenocarcinoma							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**

Pembrolizumab	2A certain circumstances in subsequent therapy	Solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options	Phase 2 (KEYNOTE-158)	N/A	ORR	Second-line or subsequent therapy	• In the phase II KEYNOTE-158 study, which enrolled 22 patients with pancreatic cancer, there were four objective responses (18%), one of which was complete, and the median duration of response was 13.4 months.
Pembrolizumab	2A certain circumstances in first-line therapy or for recurrent disease after resection	Solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options	No clinical literature to support use.				•
Bone Cancer (Ewing Sarcoma, Chondrosarcoma [excluding dedifferentiated or mesenchymal subtypes], or Osteosarcoma [excluding undifferentiated pleomorphic sarcoma])							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pembrolizumab	2A preferred	Solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options	Phase 2 (SARC028), multicenter, 2-cohort (soft tissue sarcoma & bone sarcoma), open-label	N/A	ORR	Subsequent therapy	• The primary endpoint of overall response was not met. 2 of 40 (5%) bone sarcoma patients had an objective response, including in 1 patient with osteosarcoma and another patient with chondrosarcoma.
Gastric adenocarcinoma OR esophageal/gastroesophageal junction adenocarcinoma or squamous cell carcinoma							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pembrolizumab	2A certain circumstances second-line or	Solid tumors that have progressed following prior treatment and who have no	Phase 2 (KEYNOTE-016)	N/A	ORR 20-week PFS	CRC: after at least 2 prior cancer therapy regimens	• Data from 86 patients with dMMR tumors representing 12 different cancer types, including gastroesophageal cancers, achieved

	subsequent therapy	satisfactory alternative treatment options				Non-CRC: after at least 1 prior cancer therapy	an ORR of 53% with 21% of patients achieving a complete response to pembrolizumab.
Pembrolizumab	2A certain circumstances second-line or subsequent therapy	Solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options	Phase 2 (KEYNOTE-158)	N/A	ORR	Subsequent therapy	• Pembrolizumab demonstrated a clinical benefit with an overall ORR of 34.3% in patients with previously treated unresectable or metastatic MSI-H/dMMR non-colorectal cancer. ORR for the 24 patients with gastric cancer was 45.8%.
Ovarian Cancer (epithelial ovarian, fallopian tube, and primary peritoneal cancers)							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pembrolizumab	2A certain circumstances	Solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options	Phase 2 (KEYNOTE-158)	N/A	ORR	Subsequent therapy	• Pembrolizumab demonstrated a clinical benefit with an overall ORR of 34.3% in patients with previously treated unresectable or metastatic MSI-H/dMMR non-colorectal cancer. ORR for the 15 patients with ovarian cancer was 33.3%.
Uterine Cancer (Endometrial Carcinoma)							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pembrolizumab	2A certain circumstances	Solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options	Phase 2 (KEYNOTE-158)	N/A	ORR	Subsequent therapy	• Pembrolizumab demonstrated a clinical benefit with an overall ORR of 34.3% in patients with previously treated unresectable or metastatic MSI-H/dMMR non-colorectal cancer. ORR for the 49 patients with endometrial cancer was 57.1%.

							Complete responses occurred most frequently in these patients (8 CR).
Dostarlimab	2A certain circumstances	Yes for dMMR endometrial cancer after prior platinum therapy	Phase 1 (GARNET), open-label, multi-center	N/A	ORR DOR	After prior platinum therapy	• Dostarlimab was associated with clinically meaningful and durable antitumor activity with an ORR of 42.3% for patients with deficient mismatch mutation repair endometrial cancers after prior platinum-based chemotherapy.
Penile Cancer							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pembrolizumab	2A preferred	Solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options	Phase 2 (KEYNOTE-158)	N/A	ORR	Subsequent therapy	• Pembrolizumab demonstrated a clinical benefit with an overall ORR of 34.3% in patients with previously treated unresectable or metastatic MSI-H/dMMR non-colorectal cancer. However, this study did not include patients with penile cancer.
Testicular Cancer							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pembrolizumab	2A certain circumstances	Solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options	Phase 2 (KEYNOTE-158)	N/A	ORR	Subsequent therapy	• Pembrolizumab demonstrated a clinical benefit with an overall ORR of 34.3% in patients with previously treated unresectable or metastatic MSI-H/dMMR non-colorectal cancer. This study included only one patient with testicular cancer.

Pembrolizumab	2A certain circumstances	Solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options	Phase 2 (GU14-206)	N/A	ORR	Progressed after first-line cisplatin-based chemotherapy and after at least one salvage regimen (high-dose or standard-dose chemotherapy)	• Pembrolizumab does not appear to have clinically meaningful single-agent activity in refractory germ cell tumors.
Hepatobiliary Cancer (Gallbladder cancer, Intra-/Extra-hepatic cholangiocarcinoma)							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pembrolizumab	2A certain circumstances	Solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options	Phase 2 (KEYNOTE-158)	N/A	ORR	Subsequent therapy	• Pembrolizumab demonstrated a clinical benefit with an overall ORR of 34.3% in patients with previously treated unresectable or metastatic MSI-H/dMMR non-colorectal cancer. ORR for the 2 patients with cholangiocarcinoma was 40.9% with 2 complete responses and 7 partial responses.
Vulvar Squamous Cell Carcinoma							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pembrolizumab	2A certain circumstances	Solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options	Phase 2 (KEYNOTE-158)	N/A	ORR	Subsequent therapy	• Pembrolizumab demonstrated a clinical benefit with an overall ORR of 34.3% in patients with previously treated unresectable or metastatic MSI-H/dMMR non-colorectal cancer. This study included only one patient with vulvar cancer.

Cervical Cancer							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pembrolizumab	2A preferred	Solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options	Phase 2 (KEYNOTE-158)	N/A	ORR	Subsequent therapy	• Pembrolizumab demonstrated a clinical benefit with an overall ORR of 34.3% in patients with previously treated unresectable or metastatic MSI-H/dMMR non-colorectal cancer. This study included 6 patients with cervical cancer.
Breast Cancer							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pembrolizumab	2A certain circumstances	Solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options	Phase 2 (KEYNOTE-158)	N/A	ORR	Subsequent therapy for unresectable or metastatic disease	• Pembrolizumab demonstrated a clinical benefit with an overall ORR of 34.3% in patients with previously treated unresectable or metastatic MSI-H/dMMR non-colorectal cancer. This study included 5 patients with breast cancer.
Occult Primary/Cancer of Unknown Primary (CUP)							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pembrolizumab	2A certain circumstances	Solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options	Phase 2 (KEYNOTE-158)	N/A	ORR	Subsequent therapy	• Pembrolizumab demonstrated a clinical benefit with an overall ORR of 34.3% in patients with previously treated unresectable or metastatic MSI-H/dMMR non-colorectal cancer. However, this study did not include

							any patients with cancer of unknown primary.
Small Bowel Adenocarcinoma/Advanced Ampullary Cancer							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pembrolizumab	2A	Solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options	Phase 2 (KEYNOTE-158)	N/A	ORR	Subsequent therapy	• Pembrolizumab demonstrated a clinical benefit with an overall ORR of 34.3% in patients with previously treated unresectable or metastatic MSI-H/dMMR non-colorectal cancer. This study included 6 patients with cervical cancer.
Very Advanced Squamous Cell Carcinoma of the Head and Neck (SCCHN)							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pembrolizumab	2A certain circumstances	Solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options	Phase 2 (KEYNOTE-158)	N/A	ORR	Subsequent therapy	• Pembrolizumab demonstrated a clinical benefit with an overall ORR of 34.3% in patients with previously treated unresectable or metastatic MSI-H/dMMR non-colorectal cancer. This study included 6 patients with cervical cancer.
Prostate Cancer							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pembrolizumab	2A certain circumstances	Solid tumors that have progressed following prior treatment and who have no	Phase 2 (KEYNOTE-158)	N/A	ORR	Subsequent therapy	• Pembrolizumab demonstrated a clinical benefit with an overall ORR of 34.3% in patients with previously treated unresectable or metastatic MSI-H/dMMR non-colorectal cancer.

		satisfactory alternative treatment options					This study included 6 patients with cervical cancer.
Pembrolizumab + enzalutamide	None	Solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options	Phase 2, single-institution	N/A	PSA response	Previously treated with enzalutamide	• Pembrolizumab plus enzalutamide demonstrated clinical activity with 2 out of 10 patients achieving a partial response.
Other Solid Tumor (e.g., adrenal gland tumors, poorly differentiated-high grade-neuroendocrine tumors [NET], large or small cell NET, etc.)							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pembrolizumab	2A	Solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options	Phase 2 (KEYNOTE-158)	N/A	ORR	Subsequent therapy	• Pembrolizumab demonstrated a clinical benefit with an overall ORR of 34.3% in patients with previously treated unresectable or metastatic MSI-H/dMMR non-colorectal cancer. This study included 7 patients with NET and 5 patients with adrenocortical tumors.

Vulvar Squamous Cell Carcinoma

Second-line therapy for PD-L1 positive (CPS ≥1%) disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pembrolizumab	2A	No	Case report	N/A	N/A	Recurrent disease	• Pembrolizumab demonstrated to be effective in a case report of one patient with PD-L1 positive recurrent vulvar cancer.

Thymic Carcinoma

Second-line therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pembrolizumab	2A	No	Phase 2, single-arm, single-center	N/A	ORR	Recurrent thymic carcinoma who had progressed after at least one line of chemotherapy	• Pembrolizumab is active a second-line therapy in patients with thymic carcinomas with an ORR of 22.5% but is associated with a high rate of severe immune-related adverse events (15%).
Pembrolizumab	2A	No	Phase 2	N/A	ORR	Disease progression after platinum-based chemotherapy	• In this study partial responses were seen in 5 of 26 patients (19%) with thymic carcinoma and median progression survival was 6.1 months.
Pemetrexed	2A	No	Phase 2	N/A	-----	Previously treated	• Pemetrexed is an active agent in this heavily pretreated population of patients with recurrent thymic malignancies, especially thymoma. 2 complete responses and 3 partial responses were documented.
Gemcitabine + capecitabine	2A	No	Phase 2	N/A	-----	Previously treated	• Gemcitabine plus capecitabine is active in thymic epithelial tumors with 12 patients responding to treatment.
Sunitinib	2A (thymic carcinoma only)	No	Phase 2, open-label	N/A	ORR	Chemo-refractory	• Sunitinib is active in previously treated patients with thymic carcinoma with a partial response rate of 26% and stable disease rate of 65%.
Everolimus	2A	No	Phase 2, open-label, multi-center	N/A	DCR	After cisplatin-based therapy	• Everolimus may induce durable disease control in a high percentage of patients with thymoma or thymic carcinoma after cisplatin-based chemotherapy.

Octreotide	2A	No	Phase 2	N/A	ORR	All lines of therapy	• Octreotide alone has modest activity in patients with octreotide scan-positive thymoma demonstrating an ORR of 30.3%.
Paclitaxel	2A	No	Case report	N/A	-----	After platinum-based therapy	• This is the first report to suggest that paclitaxel has anti-thymoma activity.

Chapter 2 Malignant Pleural Mesothelioma

Subsequent therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pembrolizumab	2A preferred	No	Phase 1b (KEYNOTE-028) Updated results	N/A	Safety Response	Previously treated	• Single-agent pembrolizumab has significant clinical activity in patients with PD-L1–positive MPM. Responses from pembrolizumab in patients with MPM are durable with a 62.6% 12-month OS rate in this mostly pretreated patient population
Pembrolizumab	2A preferred	No	Phase 2	N/A	-----	Second-line	• Second-line therapy with pembrolizumab demonstrated and overall ORR of 37%. Greater clinical activity was associated with high PD-L1 expression.
Pembrolizumab	2A preferred	No	Phase 3 (PROMISE-meso), randomized, open-label	Gemcitabine or vinorelbine	PFS	Second-line	• In second-line therapy, pembrolizumab was associated with an improved ORR however failed to improve PFS or OS compared to single agent chemotherapy in patients with relapsed MPM.
Pemetrexed + best supportive case (P+BSC)	1 preferred	No	Phase 3, multi-center	Best supportive care (BSC)	OS	Second-line	• Second-line pemetrexed elicited significant tumor response and delayed disease progression compared with BSC alone in patients with

							advanced MPM. Improvement in OS was not seen in this study.
Pemetrexed	1 preferred	No	Retrospective study	N/A	-----	Second-line	• In selected patients, re-challenge with pemetrexed-based regimens, preferentially associated with platinum-compound, appears to be an option for second-line therapy.
Nivolumab ± ipilimumab	2A preferred	No	Phase 2 (MAPS2), randomized Updated results	N/A	12-week DCR	Second- or third-line	• Both nivolumab and nivolumab + ipilimumab reached their endpoint in 2nd/3rd line MPM patients without any unexpected toxicity, leading to meaningful progression-free and overall survivals.
Nivolumab + ipilimumab	2A preferred	No	Phase 2 (INITIATE), single-center	N/A	12-week DCR	After at least one platinum-containing chemotherapy	• In this single-center phase 2 trial, the combination of nivolumab plus ipilimumab showed a disease control rate of 68% at 12 weeks in patients with recurrent malignant pleural mesothelioma
Nivolumab	2A preferred	No	Phase 2	N/A	12-week DCR	Recurrent MPM	• Single-agent nivolumab has meaningful clinical efficacy with a 12-week disease control rate of 47% and a manageable safety profile in pre-treated patients with mesothelioma. PD-L1 expression does not predict for response in this population.

Chapter 3 Central Nervous System Cancer

Melanoma							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**

Pembrolizumab	2A	No	Phase 2	N/A	ORR	All lines of therapy	• Pembrolizumab is active in melanoma with brain metastases with an ORR 26%.
Ipilimumab + nivolumab	2A	No	Phase 2 (CheckMate 204)	N/A	ORR	Not specified (prior therapy was allowed)	• In patients with melanoma with brain metastases, nivolumab plus ipilimumab had high intracranial anti-tumor activity with ORR 56% and CR 19%.
Ipilimumab ± nivolumab	2A	No	Phase 2, randomized	N/A	ORR	No previous local brain therapy	• Nivolumab combined with ipilimumab and nivolumab monotherapy are active in melanoma brain metastases with an ORR of 46% and 20%, respectively. A higher proportion of patients achieved an intracranial response with the combination regimen.
Ipilimumab	2A	No	Phase 2 (Cohort A: asymptomatic and no corticosteroid treatment; Cohort B: symptomatic and on corticosteroids)	N/A	Disease control	Not specified	• Ipilimumab demonstrated a disease control rate of 24% in patients with melanoma and asymptomatic brain metastases. A disease control rate of 10% was seen in patients with symptomatic brain metastases.
Non-Small Cell Lung Cancer							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pembrolizumab	2A	No	Phase 2	N/A	ORR	All lines of therapy	• Pembrolizumab demonstrated clinical activity in brain metastases in patients with NSCLC with an ORR 33%.

T-Cell Lymphoma/Extranodal NK (nasal type)

Relapsed or refractory disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pembrolizumab	2A preferred	No	Case series	N/A	-------	Second-line or subsequent therapy	• Pembrolizumab demonstrated a high response rate in patients with relapsed or refractory ENKL following treatment with asparaginase-based regimens.

Anal Carcinoma

Second-line or subsequent therapy for metastatic squamous cell disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pembrolizumab	2A preferred	No	Phase 1b (KEYNOTE-028)	N/A	Safety ORR	Failed prior standard therapy or for which standard therapy is not appropriate	• Among the 24 patients with squamous cell anal carcinoma, there were four confirmed partial responses (overall response rate 17%), and an additional 10 had stable disease as the best response (42%).
Nivolumab	2A preferred	No	Phase 2 (NCI9673), multi-center	N/A	ORR PFS	At least one prior line of therapy	• Nivolumab was effective as monotherapy for patients with metastatic squamous cell anal carcinoma with an ORR of 24%.

Gestational Trophoblastic Neoplasia

Recurrent or progressive disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**

Pembrolizumab	2A	No	Case series	N/A	--------	Second-line or subsequent therapy	• Pembrolizumab demonstrated durable responses in 3 out of 4 patients with resistant GTN.

Hepatocellular Carcinoma

Subsequent therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pembrolizumab	2B (Child-Pugh class A)	Yes	Phase 2 (KEYNOTE-224), single-arms, multicenter	N/A	ORR	After disease progression on or after sorafenib or were intolerant to sorafenib	• Pembrolizumab demonstrated an ORR of 17% in patients with advanced hepatocellular carcinoma who had previously been treated with sorafenib.
Nivolumab	2A (Child-Pugh class A or B7)	Yes	Phase 1/2 (CheckMate-040), multicenter, open-label, subgroup analysis Survival and durability of response data	Sorafenib	ORR	After disease progression on or after sorafenib or were intolerant to sorafenib	• Nivolumab demonstrated durable responses with long-term survival in both sorafenib-naïve (DOR 17 months) and sorafenib-experienced (DOR 19 months) patients with advanced HCC.
Fluorouracil + leucovorin + oxaliplatin (FOLFOX)	2B	No	Phase 3, multicenter, open-label, randomized	Doxorubicin	OS	All lines of therapy	• Although the study did not meet its primary end point, the trend toward improved OS with FOLFOX4, along with increased PFS and RR, suggests that this regimen may confer some benefit

							to patients, but an OS benefit cannot be concluded from these data.
Regorafenib	1 (Child-Pugh class A)	Yes	Phase 3 (RESORCE), randomized, double-blind, placebo-controlled	Placebo	OS	Second-line after sorafenib (excluded prior treatment for HCC except sorafenib)	• Regorafenib demonstrated a survival benefit in HCC patients progressing on sorafenib treatment.
Cabozantinib	1 (Child-Pugh class A)	Yes (Child-Pugh Class A only)	Phase 3 (CELESTIAL), randomized, double-blind	Placebo	OS	Second or third-line after sorafenib	• Among patients with previously treated advanced hepatocellular carcinoma, treatment with cabozantinib resulted in longer overall survival and progression-free survival than placebo. The rate of high-grade adverse events in the cabozantinib group was approximately twice that observed in the placebo group.
Ramucirumab	1 (AFP ≥ 400 ng/ml)	Yes (AFP ≥ 400 ng/mL only)	Phase 3 (REACH), randomized, double-blind, multi-center	Placebo	OS	Second-line after sorafenib	• In a subgroup analysis of second-line treatment of patients with advanced hepatocellular carcinoma with AFP ≥ 400 ng/mL, ramucirumab significantly improved survival over placebo.
Ramucirumab	1 (AFP ≥ 400 ng/mL only)	Yes (AFP ≥ 400 ng/mL only)	Phase 3 (REACH-2), randomized	Placebo	OS	Second-line after sorafenib	• REACH-2 met its primary endpoint, showing improved overall survival for ramucirumab compared with placebo in patients with hepatocellular carcinoma and α-fetoprotein concentrations of at least 400 ng/mL who had previously received sorafenib.
Lenvatinib	2A (Child-Pugh class A)	No	No clinical literature to support use.				

Mycosis Fungoides (MF)/Sezary Syndrome (SS)

Primary therapy for Stage III MF or Stage IV SS							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pembrolizumab	2A	No	No clinical literature evidence to support use.				
Relapsed or persistent disease for Stage III MF or Stage IV SS							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pembrolizumab	2A for stage III MF or Sezary syndrome	No	Phase 2 (CITN-10), single-arm, multi-center	N/A	ORR	Subsequent therapy (up to 4 prior therapies)	• Pembrolizumab demonstrated anti-tumor activity with an ORR of 38% with durable responses in patients with advanced MF/SS.
Liposomal doxorubicin	2A preferred (stage IV non-Sezary or visceral disease, or LCT – both primary therapy and relapsed or refractory disease)	No	Phase 2	N/A	----------	After at least one prior therapy	• Liposomal doxorubicin resulted an ORR 84% with minimal toxicity.
Liposomal doxorubicin	2A preferred (stage IV non-Sezary or visceral disease, or LCT – both primary therapy and relapsed or refractory disease)	No	Phase 2, multicenter	N/A	ORR	After at least two prior therapies	• Liposomal doxorubicin demonstrated to be effected with an ORR of 41% in patients with advanced MF
Gemcitabine	2A preferred (stage IIB MF, stage IV non-	No	Phase 2, open-label	N/A	------	After at least one prior therapy	• Gemcitabine is an effective monotherapy with a 68% overall response rate in patients with

	Sezary or visceral disease, or LCT) 2A for stage III MF or stage IV Sezary syndrome						advanced, heavily pretreated CTCL.
Bexarotene	2A preferred (stage III MF or stage IV Sezary syndrome)	Yes	Phase 2/3	N/A	ORR	Refractory to conventional therapy	• Bexarotene is effective for the treatment of advanced, refractory MF/SS with an ORR of 45-55%.

Renal Cell Carcinoma

First-line therapy for advanced, relapsed or metastatic disease with clear cell histology							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pembrolizumab + axitinib	1 preferred	Yes	Phase 3 (KEYNOTE-426), randomized, multi-center, open-label	Sunitinib	PFS OS	First-line therapy for advanced RCC	• In patients with previously untreated advanced renal-cell carcinoma, treatment with pembrolizumab plus axitinib resulted in significantly longer overall survival and progression-free survival, as well as a higher objective response rate, than treatment with sunitinib.
Pembrolizumab + lenvatinib	1 preferred	No	Phase 3 (CLEAR), randomized, open-label, multi-center	Sunitinib	PFS	First-line therapy	• Lenvatinib plus pembrolizumab was associated with significantly longer progression-free survival and overall survival than sunitinib.
Nivolumab + cabozantinib	1 preferred	Yes	Phase 3 (CheckMate 9ER), randomized, open-label	Sunitinib	PFS	First-line	• Nivolumab plus cabozantinib demonstrated superior PFS, OS, and ORR versus sunitinib in first-line advanced renal cell carcinoma.

Pazopanib	1 preferred for favorable risk 1 for poor/ intermediate risk	Yes	Phase 3 (VEG105192), open-label, double-blind, randomized, multi-center Final OS results	Placebo	PFS	First-line or after cytokine therapy	• Pazopanib demonstrated significant improvement in PFS and tumor response compared with placebo in treatment-naive and cytokine-pretreated patients with advanced and/or metastatic RCC.
Sunitinib	1 preferred for favorable risk 1 for poor/ intermediate risk	Yes	Phase 3, randomized, multi-center	IFN-α	PFS	First-line	• PFS and ORR were both significantly longer/ higher with sunitinib than IFN-α. • A trend towards OS advantage of sunitinib over IFN-α was demonstrated.
Nivolumab + ipilimumab	1 preferred for intermediate/ poor-risk 2A for favorable risk	Yes for intermediate/ poor-risk	Phase 3 (CheckMate 214), open-label, multi-center	Sunitinib	ORR PFS OS	First-line	• Overall survival and objective response rates were significantly higher with nivolumab plus ipilimumab than with sunitinib among intermediate- and poor-risk patients with previously untreated advanced renal-cell carcinoma.
Cabozantinib	2A preferred for poor/ intermediate risk 2B for favorable risk	Yes	Phase 2 (CABOSUN), open-label, randomized	Sunitinib	PFS	First-line	• Cabozantinib demonstrated a significant clinical benefit in PFS and ORR over standard-of-care sunitinib as first-line therapy in patients with intermediate- or poor-risk mRCC.
Subsequent therapy for advanced, relapsed or metastatic disease with clear cell histology							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**

Pembrolizumab + axitinib	2A	No	No clinical evidence to support use.
Pembrolizumab + lenvatinib	2A	No	No clinical evidence to support use.

Non-clear cell histology							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pembrolizumab	2A other	No	Phase 2 (KEYNOTE-427), open-label; Cohort B	N/A	ORR	First-line	• First-line pembrolizumab monotherapy demonstrated an ORR of 26.7% and duration of response of 29 months.
Nivolumab	2A	Yes after prior anti-angiogenic therapy	Retrospective study	N/A	-----	All lines of therapy	• Nivolumab monotherapy demonstrated objective responses (partial response 20% and stable disease 29%) and was well tolerated in a heterogeneous population of patients with non-clear cell mRCC.
Sunitinib	2A preferred	Yes	Phase 2 (ASPEN), multi-center, open-label, randomized	Everolimus	PFS	First-line	• In patients with metastatic non-clear cell renal cell carcinoma, sunitinib improved progression-free survival compared with everolimus.
Cabozantinib	2A preferred	No	Retrospective analysis	N/A	-----	After prior anti-angiogenic therapy	• Cabozantinib demonstrated a clinical benefit in patients with non-clear cell RCC with a median PFS of 8.6 months and median OS of 25.4 months.

Endometrial Carcinoma

Subsequent therapy

Regimen	NCCN Category	FDA Approved	Trial Design	Comparator	Primary End-Point	Line of Therapy	Conclusion
Pembrolizumab + lenvatinib	2A certain circumstances	Yes	Phase 2 (KEYNOTE-146), multi-center, open-label, single-arm	N/A	ORR	Subsequent therapy (up to 2 prior systemic therapies)	• The ORR to pembrolizumab plus lenvatinib was 36% in patients with metastatic endometrial carcinoma that was not dMMR or MSI-H, and that had progressed following at least one prior systemic therapy.
Bevacizumab + carboplatin + paclitaxel	2A (for advanced or recurrent disease only)	No	Phase 2 (MITO Group END-2 trial), randomized	Carboplatin + paclitaxel	---------	First- and second-line	• The addition of bevacizumab to carboplatin plus paclitaxel significantly increased PFS in advanced or recurrent endometrial cancer.
Bevacizumab	2A (after progression on prior cytotoxic chemo)	No	Phase 2	N/A	6-mon PFS 6-mon OS	Second- or third-line therapy	• Bevacizumab is clinically active based on PFS at 6 months of 40.4% in recurrent or persistent endometrial carcinoma
Paclitaxel	2A	No	GOG study	N/A	----------	Second-line	• Paclitaxel is an active agent in the treatment of endometrial cancer in patients who have had prior chemotherapy with an ORR of 27.3%
Liposomal doxorubicin	2A	No	Phase 2	N/A	----------	Second-line	• Liposomal doxorubicin has only limited activity (ORR 9.5%) in pretreated advanced, recurrent endometrial cancer
Temsirolimus	2A	No	Phase 2	N/A	ORR	All lines of therapy	• Temsirolimus demonstrated clinical activity with ORR higher in chemo-naïve patients than in chemo-treated patients

Soft Tissue Sarcoma

Alveolar soft part sarcoma (ASPS)							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pembrolizumab	2A	No	Retrospective analysis	N/A	-----	All lines of therapy	• All four ASPS patients had clinical benefit with checkpoint inhibitors and this was the only subtype experiencing partial response.
Undifferentiated pleomorphic sarcoma (UPS)							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pembrolizumab	2A other	No	Phase 2 (SARC028), multi-center	N/A	ORR	Subsequent therapy	• Pembrolizumab demonstrated clinical activity in patients with UPS with an ORR of 40%
Doxorubicin	2A	Yes	Phase 3, randomized, controlled	Doxorubicin + ifosfamide	OS	First-line therapy	• No significant difference in OS between groups
Gemcitabine + docetaxel	2A	No	Phase 2, open-label	Gemcitabine	ORR	0-3 prior chemotherapy regimens	• Gemcitabine-docetaxel yielded superior progression-free and overall survival to gemcitabine alone, but with increased toxicity.

Tumor Mutational Burden-High (TMB-H) Cancer

Unresectable or metastatic disease – Subsequent therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**

Pembrolizumab	2A	Yes	Phase 2 (KEYNOTE-158)	N/A	ORR	Progression on or intolerance to ≥ 1 line of standard therapy (Excluded patients with melanoma, NSCLC, & uterine sarcomas or mesenchymal tumors. CRC participants must have failed at least 2 lines of therapy)	• TMB-high was associated with higher ORR in patients with select advanced solid tumors treated with pembrolizumab monotherapy.

Cutaneous Squamous Cell Carcinoma (cSCC)

Recurrent or metastatic disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pembrolizumab	2A preferred	Yes (not candidates for surgery or radiation)	Phase 2 (KEYNOTE-629), open-label, multi-center Second interim analysis (locally advanced cohort)	N/A	ORR	Any line of therapy	• Pembrolizumab demonstrated an ORR 34.350% in patients with locally advanced cSCC and an ORR 35.2% and median duration of response was not reached in patients with recurrent or metastatic cSCC, most of whom were heavily pretreated.
Cemiplimab	2A preferred	Yes (not candidates for surgery or radiation)	Phase 2 (EMPOWER), open-label, multi-center	N/A	ORR	Untreated and previously treated	• Cemiplimab induced a response in approximately half the patients with metastatic disease.

Adrenal Gland Tumors

Adrenocortical carcinoma (ACC)							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pembrolizumab	2A	No	Phase 2	N/A	ORR	All lines of therapy	• In advanced ACC, pembrolizumab demonstrated an ORR 23% and disease control rate was 52%.
Pembrolizumab	2A	No	Phase 2, open label	N/A	NPR	Subsequent therapy	• In patients with adrenocortical carcinoma (ACC), non-pression rate at 27 weeks was 31%, ORR 15%, and clinical benefit rate was 54%.
Mitotane	2A	Yes	Case series	N/A	-----	----------	• Mitotane treatment for adrenocortical carcinoma demonstrated to be effective with total tumor resection occurring in 49% of the patients.
Mitotane + etoposide + doxorubicin + cisplatin (EDP)	2A preferred	No	Phase 2, multi-center	N/A	-----	Disease not amenable to surgery	• EDP plus mitotane in 72 adrenocortical carcinoma patients resulted an ORR of 49%.
Mitotane + etoposide + doxorubicin + cisplatin (EDP)	2A preferred	No	Phase 3 (FIRM-ACT), randomized	Mitotane + streptozocin	OS	First-line	• Rates of response and progression-free survival were significantly better with EDP plus mitotane than with streptozocin plus mitotane as first-line therapy, with similar rates of toxic events, although there was no significant difference in overall survival.

Triple Negative Breast Cancer

First-line therapy

Regimen	NCCN Category	FDA Approved	Trial Design	Comparator	Primary End-Point	Line of Therapy	Conclusion
Pembrolizumab + chemotherapy (nab-paclitaxel, paclitaxel, or gemcitabine with carboplatin)	1 preferred	Yes for PD-L1 (CPS ≥10)	Phase 3 (KEYNOTE-355), randomized, double-blind	Placebo + (nab-paclitaxel, paclitaxel, or gemcitabine with carboplatin)	PFS	First-line; ≥6 months disease free interval	• Pembrolizumab combined with several chemotherapy partners showed a statistically significant and clinically meaningful improvement in PFS vs chemo alone in patients with previously untreated locally recurrent inoperable or metastatic TNBC whose tumors expressed PD-L1 (CPS ≥10). Pembrolizumab + chemotherapy was generally well tolerated, with no new safety concerns.
Atezolizumab + nab-paclitaxel	2A preferred	Yes (for PD-L1-positive triple negative breast cancer)	Phase 3 (IMpassion130), randomized	Nab-paclitaxel + placebo	PFS OS	Treatment naïve metastatic disease	• Atezolizumab plus nab-paclitaxel prolonged progression-free survival among patients with metastatic triple-negative breast cancer in both the intention-to-treat population and the PD-L1–positive subgroup.
Subsequent therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pembrolizumab + chemotherapy (taxane or platinum-based therapy)	1	Yes for PD-L1 (CPS ≥10)	No clinical literature evidence to support use.				
Neoadjuvant/Adjuvant therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**

Pembrolizumab + paclitaxel + carboplatin, followed by pembrolizumab + doxorubicin or epirubicin + cyclophosphamide (neoadjuvant), followed by pembrolizumab (adjuvant)	TBD	Yes	Phase 3 (KEYNOTE-522), randomized, multicenter, double-blind, placebo-controlled trial	Placebo + paclitaxel + carboplatin, followed by placebo + doxorubicin or epirubicin + cyclophosphamide (neoadjuvant), followed by placebo (adjuvant)	pCR EFS	Previously untreated stage II or stage III TNBC	• Among patients with early triple-negative breast cancer, the percentage with a pathological complete response was significantly higher among those who received pembrolizumab plus neoadjuvant chemotherapy than among those who received placebo plus neoadjuvant chemotherapy.