Opdivo® (nivolumab)
(Intravenous)

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I. Length of Authorization [1,49]

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

- Adjuvant use in the treatment of melanoma can be authorized up to a maximum of 12 months of therapy.
- Use in the treatment of NSCLC in combination with ipilimumab can be authorized up to a maximum of 2 years of therapy.
- Use in the treatment of NSCLC in combination with ipilimumab and two (2) cycles of platinum-doublet chemotherapy can be authorized up to a maximum of 2 years of therapy.
- Use in the treatment of MPM as initial therapy in combination with ipilimumab can be authorized up to a maximum of 2 years of therapy.

II. Dosing Limits

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

- Opdivo 40 mg/4 mL single-use vial: 2 vials per 14 days
- Opdivo 100 mg/10 mL single-use vial: 2 vials per 14 days
- Opdivo 240 mg/24 mL single-use vial: 4 vials per 14 days

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

Indication	Billable Units (BU)	Per unit time (days)
Merkel Cell	340 BU	14 days
Melanoma/HCC (in combination with ipilimumab)	Initial: 140 BU	21 days x 4 doses
	Followed by: 480 BU	28 days
Melanoma/RCC/HCC/NSCLC (as a single agent), cHL, SCCHN, MSI-H/dMMR CRC (as a single agent), Anal Carcinoma, Esophageal Squamous Cell Carcinoma & Urothelial Carcinoma	480 BU	28 days
Metastatic NSCLC with PD-L1 expressing tumors (in combination with ipilimumab)	340 BU	14 days
Metastatic or recurrent NSCLC (in combination with ipilimumab and platinum-doublet chemotherapy	380 BU	21 days
SCLC	240 BU	14 days
	Initial: 340 BU	21 days x 4 doses

MSI-H/dMMR CRC (in combination with ipilimumab)	Followed by: 480 BU	28 days
RCC (in combination with ipilimumab)	Initial: 340 BU	21 days x 4 doses
	Followed by: 480 BU	28 days
MPM (as a single agent or in combination with ipilimumab)	340 BU	14 days
CNS Metastases from Melanoma	Initial: 140 BU	21 days x 4 doses
	Followed by: 340 BU	14 days
CNS Metastases from Melanoma (as a single agent)	340 BU	14 days

III. Initial Approval Criteria [1]

Coverage is provided for the following conditions:

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

Universal Criteria

- Patient has not received previous therapy with a programmed death (PD-1/PD-L1)-directed therapy (e.g., cemiplimab, avelumab, pembrolizumab, atezolizumab, durvalumab, etc.) prior to initiation of therapy, unless otherwise specified; **AND**

Cutaneous Melanoma † Φ [1,2,15-18,15e]

- Used as first-line therapy for unresectable or metastatic disease; **AND**
  - Used as a single agent or in combination with ipilimumab; **OR**
- Used as subsequent therapy for unresectable or metastatic* disease; **AND**
  - Used after disease progression on first-line therapy or maximum clinical benefit from BRAF-targeted therapy (e.g., dabrafenib/trametinib, vemurafenib/cobimetinib, encorafenib/binimetinib, etc.); **AND**
    - Used as a single agent; **OR**
- Used as adjuvant treatment as a single agent; **AND**
  - Patient has lymph node involvement and has undergone complete resection; **OR**
  - Patient has undergone complete resection of distant metastatic disease

**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*

Uveal Melanoma ‡ [2,19,20]

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

Hepatocellular Carcinoma (HCC) † Φ [1,2,21,39e-41e]

- Patient has locally advanced, unresectable, inoperable, or metastatic disease; **AND**
- Used as subsequent therapy; **AND**
- Patient progressed on or was intolerant to sorafenib; **AND**
  - Patient has Child-Pugh Class A or B7 disease; **AND**
    - Used as a single agent; **OR**
  - Patient has Child-Pugh Class A disease; **AND**

- Used in combination with ipilimumab

Non-Small Cell Lung Cancer (NSCLC) † [1,2,11,22,23,46,44e-46e,52e,57e,126e,128e]

- Patient has metastatic disease with a high tumor mutational burden (TMB)* (i.e., ≥10 mutations per megabase) ‡; **AND**
  - Used as a single-agent or in combination with ipilimumab as first-line therapy; **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:
      - Used in patients with PS 0-1 who have EGFR, ALK, ROS1, BRAF, MET exon skipping mutation, and RET rearrangement negative** tumors and PD-L1 expression <1%
      - Used in patients with PS 0-1 who are positive for one of the following molecular biomarkers: BRAF V600E mutations, NTRK gene fusions, MET exon 14 skipping mutations, or RET rearrangements
      - Used in patients with PS 0-2 for PD-L1 expression-positive (PD-L1 ≥1%) tumors, as detected by an FDA or CLIA compliant test❖, that are EGFR, ALK, ROS1, BRAF, MET exon skipping mutation, and RET rearrangement negative**; **AND**
      - Used in combination with:
        - Ipilimumab
        - Ipilimumab and platinum-doublet chemotherapy (e.g., pemetrexed and either carboplatin or cisplatin for non-squamous cell histology, paclitaxel and carboplatin for squamous cell histology, etc.); **OR**
  - Used as subsequent therapy; **AND**
    - Used as a single agent; **OR**
    - Used for one of the following:
      - Used in patients with PS 0-1 who have EGFR, ALK, or ROS1 positive tumors and have received prior targeted therapy§
      - Used in patients with PS 0-1 who are positive for one of the following molecular biomarkers: BRAF V600E mutations, NTRK gene fusions, MET exon 14 skipping mutations, or RET rearrangements; **AND**
      - Used in combination with:
        - Ipilimumab
        - Ipilimumab, pemetrexed, and either carboplatin or cisplatin for nonsquamous cell histology
        - Ipilimumab, paclitaxel, and carboplatin for squamous cell histology

**TMB is an evolving biomarker that may be helpful in selecting patients for immunotherapy. There is no consensus on how to measure TMB.*

** *Note: If there is insufficient tissue to allow testing for all of the EGFR, ALK, ROS1, BRAF, 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.*

Renal Cell Carcinoma (RCC) † [1,2,25,26,67e]

- Used in combination with ipilimumab for clear cell histology; **AND**
  - Used as first-line therapy in patients with advanced, relapsed, or stage IV disease with intermediate or poor risk; **OR**
  - Used as first-line therapy in patients with relapsed or stage IV disease with favorable risk; **OR**
- Used as a single agent; **AND**
  - Used as subsequent therapy in patients with advanced, relapsed, or stage IV disease for clear cell histology

Classical Hodgkin Lymphoma (cHL) † Φ [1,2,27,28,76e,78e]

- Used as a single agent; **AND**
  - Patient has received 3 or more prior lines of therapy; **OR**
  - Patient has relapsed or progressive disease after an autologous hematopoietic stem cell transplantation (HSCT) with or without brentuximab vedotin; **OR**
- Used in combination with brentuximab vedotin for relapsed or refractory disease; **AND**
  - Patient is at least 18 years old; **AND**
    - Used as second-line therapy (if not previously used); **OR**
  - Patient age is 18 years and under; **AND**
    - Used as second-line therapy; **AND**
      - Used in patients heavily pretreated (with platinum or anthracycline-based chemotherapy) or if a decrease in cardiac function observed; **OR**
    - Used as re-induction therapy; **AND**
      - Used in patients heavily pretreated (with platinum or anthracycline-based chemotherapy) or if a decrease in cardiac function observed; **OR**
      - Used with radiation therapy (ISRT) in highly favorable patients who may avoid autologous stem cell rescue (ASCR) *(i.e., initial stage other than IIIB or IVB, no prior exposure to RT, duration of CR1 >1 year, absence of extranodal disease or B symptoms at relapse)*

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

- Used as single-agent therapy; **AND**
- Patient has unresectable, recurrent, persistent, or metastatic disease; **AND**
- Disease has progressed on or after platinum-based therapy; **AND**
- Patient does not have nasopharyngeal disease; **AND**
- Patient has PD-L1 expression ≥1%

Urothelial Carcinoma (Bladder Cancer) † [1,2,30]

- Used as a single agent; **AND**
- Used as subsequent systemic therapy after previous platinum treatment*; **AND**

- Patient has one of the following diagnoses:
  - Locally advanced or metastatic urothelial carcinoma; **OR**
  - Local bladder cancer recurrence or persistent disease in a preserved bladder ‡; **OR**
  - Local or metastatic bladder cancer recurrence post-cystectomy ‡; **OR**
  - Recurrent or metastatic primary carcinoma of the urethra ‡; **AND**
    - Patient does not have recurrence of stage T3-4 disease or palpable inguinal lymph nodes; **OR**
  - Metastatic upper genitourinary (GU) tract tumors ‡; **OR**
  - Metastatic urothelial carcinoma of the prostate ‡

Note:

– *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.*

Small Cell Lung Cancer (SCLC) † Φ [1,2,24,95e,99e,100e,102e]

- Used as subsequent systemic therapy; **AND**
  - Used as a single agent for metastatic disease with progression after platinum-based treatment and at least one other line of therapy †; **OR**
  - Used as a single agent ‡; **AND**
    - Used for one of the following:
      - Used for relapse within 6 months following complete response, partial response, or stable disease with initial platinum-based treatment; **AND**
        - Patient did not relapse while on maintenance atezolizumab or durvalumab; **OR**
      - Used for primary progressive disease after platinum-based treatment

Colorectal Cancer (CRC) † [1,2,31,32,107e,108e]

- Patient is at least 12 years of age; **AND**
- Patient's disease must be microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR); **AND**
  - Used as a single agent or in combination with ipilimumab as subsequent therapy for advanced or metastatic disease that progressed following treatment with a fluoropyrimidine-, oxaliplatin-, and/or irinotecan-based chemotherapy; **OR**
  - Used as a single agent or in combination with ipilimumab as primary treatment for unresectable or metastatic disease after previous adjuvant FOLFOX (fluorouracil, leucovorin and oxaliplatin) or CapeOX (capecitabine-oxaliplatin) in the past 12 months ‡

Merkel Cell Carcinoma ‡ [2,4,33]

- Used as a single agent; **AND**
- Patient has disseminated metastatic disease

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

- Used in one of the following treatment settings:
  - 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; **AND**
- Used as a single-agent or in combination with ipilimumab for the treatment of brain metastases in patients with melanoma

Anal Carcinoma ‡ [2,6,35]

- Patient has metastatic squamous cell disease; **AND**
- Used as a single agent for subsequent therapy

Malignant Pleural Mesothelioma † ‡ [2,37,38,47]

- Used as a single agent or in combination with ipilimumab as subsequent therapy; **OR**
- Used in combination with ipilimumab as first-line therapy in patients with unresectable disease

Esophageal Squamous Cell Carcinoma (ESCC) † Φ [1,44]

- Used as a single agent; **AND**
- Used as subsequent therapy for unresectable advanced (or is not a surgical candidate), recurrent, or metastatic disease; **AND**
- Patient is refractory or intolerant to at least one prior fluoropyrimidine- and platinum-based regimen

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

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

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

Genomic Aberration/Mutational Driver Targeted Therapies (Note: *not all inclusive, refer to guidelines for appropriate use*) §
Sensitizing *EGFR* mutation-positive tumors – Afatinib – Erlotinib – Dacomitinib – Gefitinib – Osimertinib
ALK rearrangement-positive tumors – Alectinib – Brigatinib – Ceritinib

– Crizotinib – Lorlatinib
ROS1 rearrangement-positive tumors – Ceritinib – Crizotinib – Entrectinib
BRAF V600E-mutation positive tumors – Dabrafenib ± Trametinib – Vemurafenib
NTRK Gene Fusion positive tumors – Larotrectinib – Entrectinib
PD-1/PD-L1 expression-positive tumors (≥1%) – Pembrolizumab – Atezolizumab – Nivolumab ± ipilimumab
MET Exon-14 skipping mutations – Capmatinib – Crizotinib
RET rearrangement-positive tumors – Selpercatinib – Cabozantinib – Vandetanib

IV. Renewal Criteria [1,2,4-6,15-42,49]

Authorizations can be renewed based on the following criteria:

- Patient continues to meet universal and other indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified in section III; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: severe infusion reactions, complications of allogeneic hematopoietic stem cell transplantation (HSCT), severe immune-mediated adverse reactions (i.e. pneumonitis, colitis, hepatitis, endocrinopathies, nephritis/renal dysfunction, adverse skin reactions/rash, encephalitis), etc.; **AND**
- Disease response with treatment defined as stabilization of disease or decrease in size of tumor or tumor spread; **AND**

Cutaneous Melanoma (adjuvant therapy)

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

NSCLC (in combination with ipilimumab or in combination with ipilimumab and two (2) cycles of platinum-doublet chemotherapy)

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

MPM (initial therapy in combination with ipilimumab)

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

V. Dosage/Administration [1,4-6,24,31-42]

Indication	Dose

Merkel Cell	Administer 240 mg intravenously every 2 weeks or 3 mg/kg intravenously every 2 weeks until disease progression or unacceptable toxicity
Anal Cancer	Administer 240 mg intravenously every 2 weeks, 480 mg intravenously every 4 weeks, or 3 mg/kg intravenously every 2 weeks until disease progression or unacceptable toxicity
Cutaneous Melanoma	Single agent *(excluding adjuvant therapy)*: • Administer 240 mg intravenously every 2 weeks OR 480 mg intravenously every 4 weeks until disease progression or unacceptable toxicity In combination with ipilimumab *(excluding adjuvant therapy)*: • Administer 1 mg/kg intravenously, with ipilimumab on the same day, every 3 weeks for 4 doses, then follow with single agent regimen Adjuvant treatment: • Administer 240 mg intravenously every 2 weeks or 480 mg intravenously every 4 weeks until disease recurrence or unacceptable toxicity for up to 1 year
Uveal Melanoma	In combination with ipilimumab: • Administer 1 mg/kg intravenously, with ipilimumab on the same day, every 3 weeks for 4 doses, then 3 mg/kg intravenously every 2 weeks until disease progression or unacceptable toxicity
NSCLC	Single agent: • Administer 240 mg intravenously every 2 weeks OR 480 mg intravenously every 4 weeks until disease progression or unacceptable toxicity In combination with ipilimumab: • Administer 3 mg/kg intravenously every 2 weeks, with ipilimumab 1 mg/kg every 6 weeks, until disease progression or unacceptable toxicity for up to 2 years In combination with ipilimumab and platinum-doublet chemotherapy for metastatic or recurrent disease: • Administer 360 mg intravenously every 3 weeks, with ipilimumab 1 mg/kg every 6 weeks and histology-based platinum-doublet chemotherapy every 3 weeks for 2 cycles, until disease progression or unacceptable toxicity for up to 2 years
cHL, SCCHN, Urothelial Carcinoma, Esophageal Squamous Cell Carcinoma	Administer 240 mg intravenously every 2 weeks or 480 mg intravenously every 4 weeks until disease progression or unacceptable toxicity
MSI-H/dMMR CRC	Adult patients and for pediatric patients ≥ 12 years and ≥ 40 kg • **As a single agent:** Administer 240 mg intravenously every 2 weeks or 480 mg intravenously every 4 weeks until disease progression or unacceptable toxicity • **In combination with ipilimumab:** Administer 3 mg/kg intravenously, with ipilimumab 1 mg/kg on the same day, every 3 weeks for 4 doses, then follow with the single agent regimen Pediatric patients ≥ 12 years and < 40 kg • **As a single agent:** Administer 3 mg/kg intravenously every 2 weeks until disease progression or unacceptable toxicity

	• **In combination with ipilimumab:** Administer 3 mg/kg intravenously, with ipilimumab 1 mg/kg on the same day, every 3 weeks for 4 doses, then follow with the single agent regimen
SCLC	• Administer 240 mg intravenously every 2 weeks until disease progression or unacceptable toxicity
Renal Cell Carcinoma (RCC)	Single-agent: • Administer 240 mg intravenously every 2 weeks or 480 mg intravenously every 4 weeks until disease progression or unacceptable toxicity In combination with ipilimumab: • Administer 3 mg/kg intravenously, with ipilimumab on the same day, every 3 weeks for 4 doses, then follow with single-agent regimen
Hepatocellular Carcinoma (HCC)	Single-agent: • Administer 240 mg intravenously every 2 weeks or 480 mg intravenously every 4 weeks until disease progression or unacceptable toxicity In combination with ipilimumab: • Administer 1 mg/kg intravenously, with ipilimumab on the same day, every 3 weeks for 4 doses, then follow with single-agent regimen
Malignant Pleural Mesothelioma (MPM)	Single agent: • Administer 3 mg/kg intravenously every 2 weeks until disease progression or unacceptable toxicity In combination with ipilimumab: • Subsequent Therapy – Administer 3 mg/kg intravenously every 2 weeks, with ipilimumab 1 mg/kg every 6 weeks, until disease progression or unacceptable toxicity **OR** – Administer 240 mg intravenously every 2 weeks, with ipilimumab 1 mg/kg every 6 weeks (for a total of 4 ipilimumab doses); treatment with nivolumab is continued for up to 2 years or until disease progression or unacceptable toxicity • Initial Therapy – Administer 360 mg intravenously every 3 weeks, with ipilimumab 1 mg/kg every 6 weeks; treatment with nivolumab is continued for up to 2 years or until disease progression or unacceptable toxicity
CNS Metastases from Melanoma	Single agent: • Administer 3 mg/kg intravenously every 2 weeks until disease progression or unacceptable toxicity In combination with ipilimumab: • Administer 1 mg/kg intravenously, with ipilimumab on the same day, every 3 weeks for 4 doses, then 3 mg/kg intravenously every 2 weeks until disease progression or unacceptable toxicity
Dosing should be calculated using actual body weight and not flat dosing (as applicable) based on the following: Weight ≥ 74 kg:	

- Standard dose 480 mg IV every 4 weeks

Weight is 67 kg to 73 kg:

- Use 440 mg IV every 4 weeks

Weight is ≤ 66kg:

- Use 400 mg IV every 4 weeks

-OR-

Weight > 67 kg:

- Standard dose 240 mg IV every 2 weeks

Weight is 53 kg to 67 kg:

- Use 200 mg IV every 2 weeks

Weight is < 53kg:

- Use 160 mg IV every 2 weeks

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

VI. Billing Code/Availability Information

HCPCS Code:

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

NDC:

- Opdivo 40 mg/4 mL single-use vial: 00003-3772-xx
- Opdivo 100 mg/10 mL single-use vial: 00003-3774-xx
- Opdivo 240 mg/24 mL single-use vial: 00003-3734-xx

VII. References (STANDARD)

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2. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) nivolumab. National Comprehensive Cancer Network, 2020. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed November 2020.
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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
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
C06.0	Malignant neoplasm of cheek mucosa
C06.2	Malignant neoplasm of retromolar area
C06.8	Malignant neoplasm of overlapping sites of unspecified parts of mouth
C06.89	Malignant neoplasm of overlapping sites of other parts of mouth
C06.9	Malignant neoplasm of mouth, unspecified
C09.0	Malignant neoplasm of tonsillar fossa
C09.1	Malignant neoplasm of tonsillar pillar (anterior) (posterior)
C09.8	Malignant neoplasm of overlapping sites of tonsil
C09.9	Malignant neoplasm of tonsil, unspecified
C10.3	Malignant neoplasm of posterior wall of oropharynx
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
C17.0	Malignant neoplasm of duodenum
C17.1	Malignant neoplasm of jejunum
C17.2	Malignant neoplasm of ileum
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
C21.0	Malignant neoplasm of anus, unspecified
C21.1	Malignant neoplasm of anal canal
C21.2	Malignant neoplasm of cloacogenic zone
C21.8	Malignant neoplasm of overlapping sites of rectum, anus and anal canal
C22.0	Liver cell carcinoma
C22.8	Malignant neoplasm of liver, primary, unspecified as to type
C22.9	Malignant neoplasm of liver, not specified as primary or secondary
C31.0	Malignant neoplasm of maxillary sinus
C31.1	Malignant neoplasm of ethmoidal sinus
C32.0	Malignant neoplasm of glottis
C32.1	Malignant neoplasm of supraglottis
C32.2	Malignant neoplasm of subglottis
C32.3	Malignant neoplasm of laryngeal cartilage
C32.8	Malignant neoplasm of overlapping sites of larynx
C32.9	Malignant neoplasm of larynx, unspecified
C33	Malignant neoplasm of trachea
C34.00	Malignant neoplasm of unspecified main bronchus
C34.01	Malignant neoplasm of right main bronchus
C34.02	Malignant neoplasm of left main bronchus

C34.10	Malignant neoplasm of upper lobe, unspecified bronchus or lung
C34.11	Malignant neoplasm of upper lobe, right bronchus or lung
C34.12	Malignant neoplasm of upper lobe, left bronchus or lung
C34.2	Malignant neoplasm of middle lobe, bronchus or lung
C34.30	Malignant neoplasm of lower lobe, unspecified bronchus or lung
C34.31	Malignant neoplasm of lower lobe, right bronchus or lung
C34.32	Malignant neoplasm of lower lobe, left bronchus or lung
C34.80	Malignant neoplasm of overlapping sites of unspecified bronchus and lung
C34.81	Malignant neoplasm of overlapping sites of right bronchus and lung
C34.82	Malignant neoplasm of overlapping sites of left bronchus and lung
C34.90	Malignant neoplasm of unspecified part of unspecified bronchus or lung
C34.91	Malignant neoplasm of unspecified part of right bronchus or lung
C34.92	Malignant neoplasm of unspecified part of left bronchus or lung
C38.4	Malignant neoplasm of pleura
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
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
C4A.8	Merkel cell carcinoma of overlapping sites
C4A.9	Merkel cell carcinoma, unspecified
C61	Malignant neoplasm of prostate
C64.1	Malignant neoplasm of right kidney, except renal pelvis
C64.2	Malignant neoplasm of left kidney, except renal pelvis
C64.9	Malignant neoplasm of unspecified kidney, except renal pelvis
C65.1	Malignant neoplasm of right renal pelvis
C65.2	Malignant neoplasm of left renal pelvis
C65.9	Malignant neoplasm of unspecified renal pelvis
C66.1	Malignant neoplasm of right ureter
C66.2	Malignant neoplasm of left ureter
C66.9	Malignant neoplasm of unspecified ureter

C67.0	Malignant neoplasm of trigone of bladder
C67.1	Malignant neoplasm of dome of bladder
C67.2	Malignant neoplasm of lateral wall of bladder
C67.3	Malignant neoplasm of anterior wall of bladder
C67.4	Malignant neoplasm of posterior wall of bladder
C67.5	Malignant neoplasm of bladder neck
C67.6	Malignant neoplasm of ureteric orifice
C67.7	Malignant neoplasm of urachus
C67.8	Malignant neoplasm of overlapping sites of bladder
C67.9	Malignant neoplasm of bladder, unspecified
C68.0	Malignant neoplasm of urethra
C69.30	Malignant neoplasm of unspecified choroid
C69.31	Malignant neoplasm of right choroid
C69.32	Malignant neoplasm of left choroid
C69.40	Malignant neoplasm of unspecified ciliary body
C69.41	Malignant neoplasm of right ciliary body
C69.42	Malignant neoplasm of left ciliary body
C69.60	Malignant neoplasm of unspecified orbit
C69.61	Malignant neoplasm of right orbit
C69.62	Malignant neoplasm of left orbit
C76.0	Malignant neoplasm of head, face and neck
C77.0	Secondary and unspecified malignant neoplasm of lymph nodes of head, face and neck
C78.00	Secondary malignant neoplasm of unspecified lung
C78.01	Secondary malignant neoplasm of right lung
C78.02	Secondary malignant neoplasm of left lung
C78.6	Secondary malignant neoplasm of retroperitoneum and peritoneum
C78.7	Secondary malignant neoplasm of liver and intrahepatic bile duct
C78.89	Secondary malignant neoplasm of other digestive organs
C79.31	Secondary malignant neoplasm of brain
C79.51	Secondary malignant neoplasm of bone
C79.52	Secondary malignant neoplasm of bone marrow
C81.10	Nodular sclerosis Hodgkin lymphoma, unspecified site
C81.11	Nodular sclerosis Hodgkin lymphoma, lymph nodes of head, face, and neck
C81.12	Nodular sclerosis Hodgkin lymphoma, intrathoracic lymph nodes
C81.13	Nodular sclerosis Hodgkin lymphoma, intra-abdominal lymph nodes
C81.14	Nodular sclerosis Hodgkin lymphoma, lymph nodes of axilla and upper limb
C81.15	Nodular sclerosis Hodgkin lymphoma, lymph nodes of inguinal region and lower limb

C81.16	Nodular sclerosis Hodgkin lymphoma, intrapelvic lymph nodes
C81.17	Nodular sclerosis Hodgkin lymphoma, spleen
C81.18	Nodular sclerosis Hodgkin lymphoma, lymph nodes of multiple sites
C81.19	Nodular sclerosis Hodgkin lymphoma, extranodal and solid organ sites
C81.20	Mixed cellularity Hodgkin lymphoma, unspecified site
C81.21	Mixed cellularity Hodgkin lymphoma, lymph nodes of head, face, and neck
C81.22	Mixed cellularity Hodgkin lymphoma, intrathoracic lymph nodes
C81.23	Mixed cellularity Hodgkin lymphoma, intra-abdominal lymph nodes
C81.24	Mixed cellularity Hodgkin lymphoma, lymph nodes of axilla and upper limb
C81.25	Mixed cellularity Hodgkin lymphoma, lymph nodes of inguinal region and lower limb
C81.26	Mixed cellularity Hodgkin lymphoma, intrapelvic lymph nodes
C81.27	Mixed cellularity Hodgkin lymphoma, spleen
C81.28	Mixed cellularity Hodgkin lymphoma, lymph nodes of multiple sites
C81.29	Mixed cellularity Hodgkin lymphoma, extranodal and solid organ sites
C81.30	Lymphocyte depleted Hodgkin lymphoma, unspecified site
C81.31	Lymphocyte depleted Hodgkin lymphoma, lymph nodes of head, face, and neck
C81.32	Lymphocyte depleted Hodgkin lymphoma, intrathoracic lymph nodes
C81.33	Lymphocyte depleted Hodgkin lymphoma, intra-abdominal lymph nodes
C81.34	Lymphocyte depleted Hodgkin lymphoma, lymph nodes of axilla and upper limb
C81.35	Lymphocyte depleted Hodgkin lymphoma, lymph nodes of inguinal region and lower limb
C81.36	Lymphocyte depleted Hodgkin lymphoma, intrapelvic lymph nodes
C81.37	Lymphocyte depleted Hodgkin lymphoma, spleen
C81.38	Lymphocyte depleted Hodgkin lymphoma, lymph nodes of multiple sites
C81.39	Lymphocyte depleted Hodgkin lymphoma, extranodal and solid organ sites
C81.40	Lymphocyte-rich Hodgkin lymphoma, unspecified site
C81.41	Lymphocyte-rich Hodgkin lymphoma, lymph nodes of head, face, and neck
C81.42	Lymphocyte-rich Hodgkin lymphoma, intrathoracic lymph nodes
C81.43	Lymphocyte-rich Hodgkin lymphoma, intra-abdominal lymph nodes
C81.44	Lymphocyte-rich Hodgkin lymphoma, lymph nodes of axilla and upper limb
C81.45	Lymphocyte-rich Hodgkin lymphoma, lymph nodes of inguinal region and lower limb
C81.46	Lymphocyte-rich Hodgkin lymphoma, intrapelvic lymph nodes
C81.47	Lymphocyte-rich Hodgkin lymphoma, spleen
C81.48	Lymphocyte-rich Hodgkin lymphoma, lymph nodes of multiple sites
C81.49	Lymphocyte-rich Hodgkin lymphoma, extranodal and solid organ sites
C81.70	Other Hodgkin lymphoma unspecified site
C81.71	Other Hodgkin lymphoma lymph nodes of head, face, and neck
C81.72	Other Hodgkin lymphoma intrathoracic lymph nodes

C81.73	Other Hodgkin lymphoma intra-abdominal lymph nodes
C81.74	Other Hodgkin lymphoma lymph nodes of axilla and upper limb
C81.75	Other Hodgkin lymphoma lymph nodes of inguinal region and lower limb
C81.76	Other Hodgkin lymphoma intrapelvic lymph nodes
C81.77	Other Hodgkin lymphoma spleen
C81.78	Other Hodgkin lymphoma lymph nodes of multiple sites
C81.79	Other Hodgkin lymphoma extranodal and solid organ sites
C81.90	Hodgkin lymphoma, unspecified site
C81.91	Hodgkin lymphoma, unspecified lymph nodes of head, face, and neck
C81.92	Hodgkin lymphoma, unspecified intrathoracic lymph nodes
C81.93	Hodgkin lymphoma, unspecified intra-abdominal lymph nodes
C81.94	Hodgkin lymphoma, unspecified lymph nodes of axilla and upper limb
C81.95	Hodgkin lymphoma, unspecified lymph nodes of inguinal region and lower limb
C81.96	Hodgkin lymphoma, unspecified intrapelvic lymph nodes
C81.97	Hodgkin lymphoma, unspecified spleen
C81.98	Hodgkin lymphoma, unspecified lymph nodes of multiple sites
C81.99	Hodgkin lymphoma, unspecified extranodal and solid organ sites
D09.0	Carcinoma in situ of bladder
D37.01	Neoplasm of uncertain behavior of lip
D37.02	Neoplasm of uncertain behavior of tongue
D37.05	Neoplasm of uncertain behavior of pharynx
D37.09	Neoplasm of uncertain behavior of other specified sites of the oral cavity
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
Z85.038	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
Z85.21	Personal history of malignant neoplasm of larynx
Z85.22	Personal history of malignant neoplasm of nasal cavities, middle ear, and accessory sinuses
Z85.51	Personal history of malignant neoplasm of bladder
Z85.59	Personal history of malignant neoplasm of other urinary tract organ
Z85.71	Personal history of Hodgkin lymphoma
Z85.810	Personal history of malignant neoplasm of tongue
Z85.818	Personal history of malignant neoplasm of other sites of lip, oral cavity and pharynx
Z85.819	Personal history of malignant neoplasm of unspecified site of lip, oral cavity and pharynx
Z85.820	Personal history of malignant melanoma of skin

Z85.821	Personal history of Merkel cell carcinoma

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):

Jurisdiction(s): 6, K	**NCD/LCD/Article Document (s):** A54862
https://www.cms.gov/medicare-coverage-database/search/article-date-search.aspx?DocID=A54862&bc=gAAAAAAAAAAAAA==	

Jurisdiction(s): J&M	**NCD/LCD/Article Document (s):** A56141
https://www.cms.gov/medicare-coverage-database/search/article-date-search.aspx?DocID=A56141&bc=gAAAAAAAAAAA	

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; CMR = complete metabolic response

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**
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.
Nivolumab + ipilimumab	1 preferred	Yes	Pooled Analysis of CheckMate-067 and 069	Nivolumab Ipilimumab	-----	First-line	• A longer treatment-free survival without toxicity was observed for patients with previously untreated advanced melanoma who received nivolumab plus ipilimumab compared with nivolumab or ipilimumab.

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.
Subsequent therapy for unresectable or metastatic disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Nivolumab	2A preferred	Yes	Phase 3 (CheckMate 037), randomized, controlled, open-label	Investigator's choice chemotherapy (dacarbazine, carboplatin/ paclitaxel)	ORR OS	Second-line or subsequent therapy after ipilimumab and if BRAFV600 mutant-positive, a BRAF inhibitor	• Nivolumab demonstrated higher, more durable responses but no difference in survival compared with chemotherapy.
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.
Ipilimumab (± gp100 vaccine)	2A 2B (in combination with	Yes	Phase 3 (CA184-002), randomized, double-blind, double-dummy	Gp100 vaccine	OS	Second-line or subsequent therapy. Patients with progression after	• Ipilimumab, with or without a gp100 peptide vaccine, as compared with gp100 alone, improved overall survival in patients with previously

	talimogene laherparepvec)					showing initial clinical benefit (PR, CR, or stable disease ≥ 3 months duration after week 12) were eligible for reinduction therapy.	treated metastatic melanoma. Adverse events can be severe, long-lasting, or both, but most are reversible with appropriate treatment.
Nab-paclitaxel	2A	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	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	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	No	Retrospective analysis	N/A	----------	Second-line	• Paclitaxel + carboplatin demonstrated clinical activity 26% partial responses and 19% having stable disease
Temozolomide	2A	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	No	Phase 2	N/A	----------	----------	• Taxol has activity in melanoma with an ORR of 14%
Dacarbazine	2A	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 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)	Yes (with involvement of lymph node(s) following complete resection)	Phase 3 (KEYNOTE-054), double-blind, randomized	Placebo	RFS	Adjuvant therapy for completely resected stage III disease	• At a median follow-up of 1.2 years, pembrolizumab improved RFS and reduced risk of distant metastases; OS 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 recurrence or unacceptable toxicities)	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 undergone complete resection, including total lymphadenec-tomy)	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 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	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.

	TLDN and/or complete resection of nodal recurrence) 2A 2B (if NED after initial treatment with local or regional therapy)						

Uveal Melanoma

Distant metastatic disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
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%.
Pembrolizumab	2A	No	Case report (10 patients)	N/A	N/A	Subsequent therapy	• Pembrolizumab demonstrated a PFS of 18 weeks in patients with metastatic uveal melanoma. Out of 8

						after prior ipilimumab	evaluable patients, there were 1 complete response, 2 partial response, and 1 patient with stable disease.
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.				

Hepatocellular Carcinoma (HCC)

Subsequent therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
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.
Nivolumab + ipilimumab (3 different dosing schedules)	2A (Child-Pugh class A)	Yes	Phase 1/2 (CheckMate-040), randomized	N/A	Safety Tolerability	After disease progression on or after sorafenib or were intolerant to sorafenib	• Nivolumab + ipilimumab led to clinically meaningful responses and had an acceptable safety profile in sorafenib-treated patients, with an ORR twice that of nivolumab monotherapy (31% and 14%, respectively).
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.
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.				

Non-Small Cell Lung Cancer (NSCLC)

Metastatic disease with high tumor mutational burden (TMB)							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
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.
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**
Nivolumab + ipilimumab	2A certain circumstances (PD-L1 ≥1%) or other	Yes for PD-L1 ≥1%	Phase 3 (CheckMate-227), randomized, open-label	Platinum-doublet chemotherapy	OS PFS	First-line	• First-line treatment with nivolumab plus ipilimumab resulted in a longer duration of overall survival than did chemotherapy in patients with NSCLC, independent of the PD-L1 expression level.

Nivolumab + ipilimumab + 2 cycles platinum doublet chemotherapy	2A other	Yes	Phase 3 (CheckMate-9LA), randomized	Chemotherapy	OS	First-line	• CheckMate 9LA met its primary endpoint. A statistically significant improvement in OS was observed with nivolumab + ipilimumab + chemotherapy versus chemotherapy alone in first-line advanced NSCLC.
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 fusion positive tumors)	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
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	2A 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%.
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), multi-center, open-label	N/A	ORR	Previously untreated and treated patients	• In previously untreated patients with BRAF V600E-positive NSCLC, 4 out of 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	N/A	ORR DOR	TRK inhibitor-naïve	• Entrectinib induced clinically meaningful responses in patients with NTRK-FP solid tumors,

			and ALKA-372-001)				including those with NSCLC (ORR 70%).
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**
Nivolumab + ipilimumab	2A certain circumstances (PD-L1 ≥1%) or other	Yes for PD-L1 ≥1%	Phase 3 (CheckMate-227), randomized, open-label	Platinum-doublet chemotherapy	OS PFS	First-line	• First-line treatment with nivolumab plus ipilimumab resulted in a longer duration of overall survival than did chemotherapy in patients with NSCLC, independent of the PD-L1 expression level.
Nivolumab + ipilimumab + 2 cycles platinum doublet chemotherapy	2A other	Yes	Phase 3 (CheckMate-9LA), randomized	Chemotherapy	OS	First-line	• CheckMate 9LA met its primary endpoint. A statistically significant improvement in OS was observed with nivolumab + ipilimumab + chemotherapy versus chemotherapy alone in first-line advanced NSCLC.
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	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

	V600E-mutation positive or NTRK gene 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	2A 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%.
Atezolizumab + carboplatin + paclitaxel + bevacizumab (ABCP), followed by atezolizumab, bevacizumab, or both	1 (for adeno-carcinoma only; PS 0-1)	Yes	Phase 3 (IMpower150), open-label, randomized (1:1:1)	Atezolizumab + carboplatin + paclitaxel (ACP), followed by atezolizumab vs. bevacizumab + carboplatin + paclitaxel (BCP), followed by bevacizumab	PFS	First-line	• The addition of atezolizumab to bevacizumab plus chemotherapy significantly improved progression-free survival and overall survival among patients with metastatic nonsquamous NSCLC, regardless of PD-L1 expression and EGFR or ALK genetic alteration status

Atezolizumab + carboplatin + nab-paclitaxel, followed by maintenance atezolizumab	2A	Yes	Phase 3 (IMpower130), randomized, multi-center, open-label	Carboplatin + paclitaxel	PFS OS	First-line for stage IV disease	• IMpower130 showed a significant and clinically meaningful improvement in overall survival and a significant improvement in progression-free survival with atezolizumab plus chemotherapy versus chemotherapy as first-line treatment of patients with stage IV non-squamous non-small-cell lung cancer and no ALK or EGFR mutations.
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), multi-center, open-label	N/A	ORR	Previously untreated and treated patients	• In previously untreated patients with BRAF V600E-positive NSCLC, 4 out of 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,	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.

			SCOUT, and NAVIGATE)				
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%).
Subsequent therapy for recurrent, advanced, or metastatic disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
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)	Yes	Phase 3 (CheckMate 057),	Docetaxel	OS	Subsequent	• Among patients with advanced nonsquamous NSCLC that had progressed during or after

	2A (for subsequent progression)		randomized, open-label				platinum-based chemotherapy, overall survival was longer with nivolumab than with docetaxel
Pembrolizumab (2 mg/kg vs. 10 mg/kg)	1 preferred (first progression) 2A (subsequent progression)	Yes (PD-L1 ≥1% with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving pembrolizumab)	Phase 2/3 (KEYNOTE-010), randomized, multicenter, open-label, active-controlled trial	Docetaxel	OS PFS	Previously treated	• Pembrolizumab prolongs overall survival in patients with previously treated, PD-L1-positive, advanced non-small-cell lung cancer.
Atezolizumab	1 (for first progression) 2A (for subsequent progression)	Yes (after platinum therapy)	Phase 3 (OAK), open-label, multicenter randomized (1:1)	Docetaxel	OS	Second- or third-line	• Atezolizumab treatment results in a statistically significant and clinically 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	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.

		on or intolerant to crizotinib					
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

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**
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.
Pembrolizumab + axitinib	1 for poor or intermediate risk 2A preferred for favorable risk	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.
Pazopanib	1 preferred for favorable risk	Yes	Phase 3 (VEG105192), open-label, double-blind,	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-

	1 for poor/ intermediate risk		randomized, multi-center Final OS results				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.
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 – Clear cell histology							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Nivolumab	1 preferred	Yes after prior anti-angiogenic therapy	Phase 3 (CheckMate-025), randomized	Everolimus	OS	After prior anti-angiogenic therapy	• This phase 3 randomized study demonstrated that patients with advanced renal cell carcinoma experienced longer survival with nivolumab treatment than with everolimus treatment after prior antiangiogenic treatment.
Nivolumab + ipilimumab	2A preferred	No	Phase 1b (CheckMate-	N/A	Safety	After one prior treatment	• Nivolumab plus ipilimumab demonstrate safety and durable response in patients with clear cell

			016), open-label, dose-escalation study				advanced or metastatic RCC, regardless of risk.
Cabozantinib	1 preferred	Yes	Phase 3 (METEOR)	Everolimus	PFS	After prior anti-angiogenic therapy	• Cabozantinib improved progression-free survival compared to everolimus in RCC patients who progressed after VEGFR-targeted therapy.
Pembrolizumab + axitinib	2A	No	No clinical evidence to support use.				
Subsequent therapy for advanced, relapsed or metastatic disease – Non-clear cell histology							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Nivolumab	2A	Yes after prior anti-angiogenic therapy	Retrospective study	N/A	-----	-------	• 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	1 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 other recommended	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.

Everolimus	2A other recommended	No	Expanded-access trial (REACT)	N/A	-----	After prior anti-angiogenic therapy	• Approximately 50% of patients with metastatic non-clear cell RCC achieved disease control with everolimus.

Classic Hodgkin Lymphoma (cHL)

Relapsed or refractory disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
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 + nivolumab (up to 4 cycles)	2A	No	Phase 1/2	N/A	CR	Initial salvage therapy	• The combination of brentuximab vedotin and nivolumab demonstrated an ORR of 82% as initial salvage therapy.
Brentuximab + nivolumab (up to 4 cycles) *Ongoing*	2A	No	Phase 2 (CheckMate 744)	N/A	CMR rate	Relapsed or refractory disease	• Brentuximab plus nivolumab demonstrated high complete metabolic response rates with no new safety signals for younger patients with relapsed or refractory cHL.

Brentuximab vedotin + gemcitabine (4 cycles)	2A (pediatric)	No	Phase 2	N/A	CR	Relapsed or refractory disease	• Brentuximab vedotin with gemcitabine demonstrated a CR rate of 57% for pediatric and young adults patients with primary refractory or early relapse Hodgkin's lymphoma.
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 + brentuximab vedotin	2A (second-line or subsequent therapy)	No	Phase 1-2, multi-center	N/A	ORR	Relapsed or refractory disease after at least one previous line of chemo	• This study shows that brentuximab vedotin plus bendamustine, with a favorable safety profile, is an active salvage regimen for heavily pretreated patients with relapsed or refractory Hodgkin's lymphoma
Pembrolizumab	2A for 3rd-line or subsequent therapy (≥ 18 years) 2A for palliative therapy (> 60 years)	Yes (pediatric and adults)	Phase 2 (KEYNOTE-087) 2-year follow-up	N/A	ORR	After ASCT with or without brentuximab vedotin or after salvage chemotherapy and brentuximab vedotin (chemo-resistant disease and ineligible for ASCT)	• Among heavily pretreated patients with relapsed or refractory cHL who received pembrolizumab, median PFS was 14 months; for patients who achieved a complete response, two-year PFS was >60 percent.

Pembrolizumab	2A (subsequent therapy)	Yes (after 3 or more prior lines of therapy)	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.
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.

Squamous Cell Carcinoma of the Head and Neck (SCCHN)

Subsequent therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Nivolumab	1 preferred	Yes after platinum-based therapy	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	1 preferred	Yes	Phase 3 (KEYNOTE-040), randomized, open-label PD-L1 results	Investigator's choice (methotrexate, docetaxel, cetuximab)	OS	After platinum-based chemo for recurrent or metastatic disease	• Pembrolizumab improved OS compared to the standard of care arm (methotrexate, docetaxel, or cetuximab) 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%.

Bladder Cancer/Urothelial Carcinoma

Relapsed or refractory disease (platinum-refractory)

Regimen	NCCN Category	FDA Approved	Trial Design	Comparator	Primary End-Point	Line of Therapy	Conclusion
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.
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-	• Avelumab showed antitumor activity in the treatment of patients with platinum-refractory metastatic urothelial carcinoma with an 6-month ORR of 17%.

						containing neoadjuvant or adjuvant chemotherapy	
Atezolizumab	2A alternative preferred	Yes	Phase 2 (IMvigor210 – Cohort 2), single-arm, multicenter	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 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.
Durvalumab	2A alternative preferred	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.

Small Cell Lung Cancer

Subsequent therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Nivolumab ± ipilimumab	2A (single agent nivolumab) Not recommended (nivolumab + ipilimumab)	Yes (single-agent nivolumab only)	Phase 1/2 (CheckMate 032)	N/A	ORR	After at least one previous platinum-regimen	• Nivolumab monotherapy and nivolumab plus ipilimumab showed ant-tumor activity with an ORR of 10% and 19%-23%, respectively.
Nivolumab	2A	Yes	Phase 3 (CheckMate 331), randomized	Chemotherapy (topotecan or amrubicin)	OS	After at least one previous platinum-regimen	• No statistically significant improvement in OS was seen with nivolumab versus chemotherapy patients with relapsed SCLC after first-line, platinum-based chemotherapy.
Pembrolizumab	2A	Yes	Combined analysis (KEYNOTE-028 [phase 1b] & KEYNOTE-158 [phase 2])	N/A	ORR	Third-line or later therapy	• Pembrolizumab demonstrated an ORR 19.3% and a median OS of 7.7 months.
Topotecan (IV)	2A preferred	Yes	Phase 3, randomized	Cyclophosphamide + doxorubicin + vincristine (CAV)		Relapsed SCLC	• Single-agent intravenous topotecan had similar response rates and survival compared to CAV in the treatment patients with recurrent SCLC and also resulted in improved control of several symptoms.

Topotecan (oral) + best supportive care	2A preferred	Yes	Phase 3	Best supportive care (BSC)	OS	Relapsed SCLC	• Chemotherapy with oral topotecan is associated with prolongation of survival in patients with relapsed SCLC.
Paclitaxel	2A	No	Phase 2	N/A	ORR	Refractory or relapsed SCLC	• Paclitaxel was effective in treating relapsed and refractory SCLC with ORR 24%.
Paclitaxel	2A	No	Phase 2	N/A	------	Refractory SCLC	• Paclitaxel is clinically active in drug-resistant SCLC with demonstrating an ORR 29%.
Docetaxel	2A	No	Phase 2	N/A	------	Previously treated SCLC	• Docetaxel demonstrated clinical activity in previously-treated patients with SCLC with ORR 25%.
Irinotecan	2A	No	Phase 2	N/A	------	Refractory or relapsed SCLC	• Irinotecan is an active agent against refractory or relapsed SCLC with ORR 47%.
Temozolomide	2A	No	Phase 2	N/A	ORR	Refractory or relapsed SCLC	• Temozolomide has activity (ORR 23%) in relapsed SCLC, particularly for brain metastases. Response to temozolomide may correlate with MGMT methylation in SCLC.

Colorectal Cancer (CRC)

First-line therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Nivolumab + ipilimumab,	2A	No	Phase 2 (CheckMate-142)	N/A	ORR	First-line	• ORR was found to be 60% in patients with previously untreated MSI-H/dMMR metastatic CRC.

followed by nivolumab			Follow-up data in first-line therapy				
Nivolumab	2A	No	No clinical literature to support use.				
Subsequent therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
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.
Adjuvant therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Nivolumab	2A	No	No clinical literature to support use.				

Merkel Cell Carcinoma

Locally advanced or metastatic disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
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%.

Pembrolizumab	2A preferred	Yes	Phase 2 (KEYNOTE-017), multi-center, open0label	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

Central Nervous System Cancer

Brain Metastases from Melanoma							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
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.
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	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.
Brain Metastases from Non-Small Cell Lung Cancer – PD-L1 positive							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Nivolumab	2A	No	Retrospective study	N/A	ORR	Not specified	• Nivolumab for patients with brain metastases from NSCLC demonstrated an intracerebral ORR 9% and PFS 3.9 months in a retrospective multi-institutional study.
Nivolumab	2A	No	Phase 2 (CheckMate 063)	N/A		Third-line or later therapy for NSCLC	• Analyses of CheckMate 063 showed that nivolumab for patients with previously treated brain metastases from NSCLC is well-tolerate, though results from analyses are currently only reported in abstract form.

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%.

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**
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%.
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%).

Gestational Trophoblastic Neoplasia

Recurrent or progressive disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Nivolumab	2A	No	No clinical literature to support use.				
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.

Malignant Pleural Mesothelioma

First-line therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Nivolumab + ipilimumab	**TBD**	No	Phase 3 (CheckMate 743), randomized, open-label	Pemetrexed + cisplatin or carboplatin	OS	First-line	• CheckMate 743 demonstrated a statistically significant improvement in OS for patients randomized to OPDIVO in combination with ipilimumab compared to chemotherapy.
Subsequent therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Nivolumab ± ipilimumab	2A	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	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	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.

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	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	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.

Small Bowel Adenocarcinoma

Initial Therapy for Advanced or Metastatic Disease – microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**

Nivolumab + ipilimumab, followed by nivolumab	2A	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.
Subsequent Therapy for Advanced or Metastatic Disease – microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
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.
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.

Extranodal NK/ T-Cell Lymphoma

Relapsed or Refractory Disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Nivolumab	2A preferred	No	No clinical literature to support use.				
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.

Esophageal Squamous Cell Carcinoma

Relapsed or Refractory Disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Nivolumab	1	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,

Endometrial Carcinoma (dMMR)

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

Nivolumab	2A certain circumstances	No	Phase 2 (NCI-MATCH Study) – Arm Z1D	N/A	ORR	Relapsed or refractory disease	• Nivolumab demonstrated an ORR of 36% in patients with dMMR refractory cancers. 13 out of 42 patients had endometrial adenocarcinoma.

Vulvar Cancer (Squamous Cell Carcinoma)

Second Line Therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Nivolumab	2A certain circumstances for HPV-related disease	No	Phase 2 (CheckMate 358)	N/A	ORR	Any line of therapy (80% of vaginal/vulvar patients had received prior systemic therapy); HPV-negative tumors were ineligible	• Nivolumab demonstrated an ORR of 20% (1 patient) in patients with recurrent or metastatic vaginal or vulvar cancers.