Yervoy® (ipilimumab)
(Intravenous)

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I. Length of Authorization

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

Renal Cell Carcinoma (RCC)/Cutaneous Melanoma (*excluding adjuvant therapy*)/Colorectal Cancer (CRC)/Hepatocellular Carcinoma (HCC)/Uveal Melanoma/CNS metastases from Melanoma (combination therapy with nivolumab) [1,6,9,10,11,17-19,20,27,29,33]

- Coverage will be provided for 12 weeks (may be extended to 16 weeks if 4 doses were not administered within the 12 week time frame) and may not be renewed*.
  * *Requests for Cutaneous Melanoma may be renewed if the patient meets the provisions for re-induction therapy.*

Non-Small Cell Lung Cancer (NSCLC)/ Malignant Pleural Mesothelioma [1,12,24]

- Coverage will be provided for up to a maximum of 2 years of therapy.

Cutaneous Melanoma (adjuvant therapy) [1,6,17]

- Coverage for adjuvant treatment will be provided for six months and may be renewed for up to a maximum of 3 years of therapy.

CNS metastases from Melanoma (single agent therapy) [8,28]

- Coverage will be provided for 12 weeks initially (may be extended to 16 weeks if 4 doses were not administered within the 12 week time frame). Coverage may be renewed in 6 month intervals thereafter.

II. Dosing Limits

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

- Yervoy 200 mg/40 mL injection:
  - 5 vials per 84 days (initially up to 5 vials per 21 days x 4 doses)
- Yervoy 50 mg/10 mL injection:
  - 3 vials per 84 days (initially up to 3 vials per 21 days x 4 doses)

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

Indication	Billable Units (BU)	Per unit time (days)
Cutaneous Melanoma (excluding adjuvant therapy)	350 BU	21 days x 4 doses
Cutaneous Melanoma (adjuvant therapy), CNS metastases from melanoma	Initial: 1150 BU	Initial: 21 days x 4 doses
	Followed by: 1150 BU	Followed by: 84 days
Uveal Melanoma	1150 BU	21 days x 4 doses
CRC, RCC, SBA	115 BU	21 days x 4 doses
MPM, NSCLC	115 BU	42 days
HCC	350 BU	21 days x 4 doses

III. Initial Approval Criteria [1]

Coverage is provided in the following conditions:

- Patient is at least 18 years of age, unless otherwise indicated; **AND**

Cutaneous Melanoma † Φ [1,2,6,17,5e,8e,21e-23e]

- Used as first-line therapy for unresectable or metastatic disease in combination with nivolumab; **OR**
- Used for unresectable or metastatic disease previously treated with cytotoxic chemotherapy as a single agent in patients at least 12 years of age †; **OR**
- Used as subsequent therapy for unresectable or metastatic* disease; **AND**
    - Used after disease progression on first-line therapy or after maximum clinical benefit from BRAF-targeted therapy (e.g., dabrafenib/trametinib, vemurafenib/cobimetinib, encorafenib/binimetinib, etc.); **AND**
        - Used in combination with pembrolizumab for patients who progress on single agent anti-PD-1 immunotherapy; **OR**
    - Used for retreatment of disease as re-induction as a single agent in patients who experienced disease control *(i.e., complete or partial response or stable disease)* from prior checkpoint inhibitor therapy, but subsequently have disease progression/relapse > 3 months after treatment discontinuation; **AND**
        - Patient has completed initial induction (i.e., completion of 4 cycles within a 16 week period); **OR**
- Used as a single-agent for adjuvant therapy; **AND**
    - Patient has stage III disease with pathologic involvement of regional lymph nodes of more than 1 mm and has undergone complete resection including total lymphadenectomy †

**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 ‡ [2,20-23,32]

- Patient has distant metastatic disease; **AND**
- Used as a single agent or in combination with nivolumab

Renal Cell Carcinoma (RCC) † [1,2,18]

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

Non-Small Cell Lung Cancer (NSCLC) † [2,12,16,24,36,35e-37e,43e,50e,89e]

- 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, NTRK1/2/3 gene fusion, MET exon 14 skipping mutation, and RET rearrangement negative** tumors and PD-L1 <1%
            - Used in patients with PS 0-1 who are positive for one of the following molecular biomarkers: BRAF V600E-mutations, NTRK1/2/3 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, NTRK1/2/3 gene fusion, MET exon 14 skipping, and RET rearrangement negative**; **AND**
        - Used in combination with:
            - Nivolumab; **OR**
            - Nivolumab and platinum-doublet chemotherapy (e.g., pemetrexed and either carboplatin or cisplatin for nonsquamous cell histology, paclitaxel and carboplatin for squamous cell histology, etc.); **OR**
    - Used as subsequent therapy; **AND**
        - Used for one of the following:
            - Used in patients with PS 0-1 who have EGFR, ALK, 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, NTRK1/2/3 gene fusions, MET exon 14 skipping mutations, or RET rearrangements; **AND**
        - Used in combination with:
            - Nivolumab

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

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

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

Malignant Pleural Mesothelioma † ‡ [2,5,25,26,34,37]

- Used in combination with nivolumab; **AND**
  - Used as subsequent therapy; **OR**
  - Used as first-line therapy in patients with unresectable disease

Central Nervous System (CNS) Cancer ‡ [2,4,8,10,11,27,82e]

- Used for the treatment of brain metastases in patients with melanoma; **AND**
- Used in combination with nivolumab or as a single agent; **AND**
- 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

Colorectal Cancer † [1,2,19,31,85e-87e]

- 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 in combination with nivolumab; **AND**
- Used in one of the following treatment settings:
  - Used as subsequent therapy for advanced or metastatic disease that progressed following treatment with a fluoropyrimidine-, oxaliplatin-, and/or irinotecan-based chemotherapy † ‡
  - Used as primary treatment for unresectable or medically inoperable, advanced, or metastatic disease* ‡
  - Used as primary treatment for unresectable liver and/or lung metastases ‡

– Used as primary treatment for unresectable metastatic disease after previous adjuvant therapy with FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) within the past 12 months ‡

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

Hepatocellular Carcinoma (HCC) † [1,2,30,30e,31e,33e,34e]

- Patient has locally advanced, unresectable, inoperable, or metastatic disease; **AND**
- Patient progressed on or was intolerant to sorafenib; **AND**
- Patient has Child-Pugh Class A disease; **AND**
- Used in combination with nivolumab; **AND**
- Patient has not previously received treatment with a checkpoint inhibitor (e.g., nivolumab, pembrolizumab, etc.)

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; 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 [1,2,6,9-12,17-29]

Coverage 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: immune-mediated reactions (e.g., diarrhea/colitis, hepatitis, dermatitis/skin adverse reactions, neuropathies, pneumonitis, nephritis/renal dysfunction, encephalitis, endocrinopathies [i.e., hypophysitis, hypothyroidism, hyperthyroidism, adrenal insufficiency] and ocular toxicity, etc.), severe infusion reactions, complications of allogeneic hematopoietic stem cell transplant, etc.; **AND**
- Disease response with treatment as defined by stabilization of disease or decrease in size of tumor or tumor spread; **AND**
- Coverage may <u>not</u> be renewed for the following indications:
  - Renal Cell Carcinoma (RCC)
  - Colorectal Cancer (CRC)
  - Hepatocellular Carcinoma (HCC)
  - Cutaneous Melanoma *(excluding adjuvant therapy)*
  - Uveal Melanoma
  - CNS metastases from melanoma (combination therapy with nivolumab)

Cutaneous Melanoma Re-induction ‡

- *Refer to Section III for criteria (see Melanoma – Used for retreatment of disease as re-induction)*

Cutaneous Melanoma Maintenance therapy (adjuvant treatment)

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

Non-Small Cell Lung Cancer (NSCLC)

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

MPM

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

V. Dosage/Administration [1,6,8-12,17-29,33,34]

Indication	Dose
Cutaneous Melanoma *(excluding adjuvant therapy)*	Single agent or in combination with nivolumab: – Administer 3 mg/kg intravenously every 3 weeks for a maximum of 4 doses In combination with pembrolizumab as subsequent therapy: Administer 1 mg/kg intravenously every 3 weeks for a maximum of 4 doses (given in combination with pembrolizumab, then follow with pembrolizumab monotherapy for up to 2 years)
Cutaneous Melanoma (adjuvant therapy)	Administer 10 mg/kg intravenously every 3 weeks for 4 doses, followed by 10 mg/kg intravenously every 12 weeks for up to 3 years
Uveal Melanoma	Single agent: – Administer 3 mg/kg or 10mg/kg intravenously every 3 weeks for 4 doses In combination with nivolumab: – Administer 3 mg/kg intravenously 3 weeks for 4 doses (given in combination with nivolumab, then follow with nivolumab monotherapy)
CNS metastases from melanoma	Single agent: – Initial: Administer 10 mg/kg intravenously every 3 weeks for 4 doses – Subsequent (starting at week 24): Administer 10 mg/kg intravenously every 12 weeks until disease progression or unacceptable toxicity In combination with nivolumab: – Administer 3 mg/kg intravenously every 3 weeks for 4 doses (given in combination with nivolumab, then follow with nivolumab monotherapy)
Hepatocellular Carcinoma (HCC)	Administer 3 mg/kg intravenously every 3 weeks for a total of 4 doses (given in combination with nivolumab, then follow with nivolumab monotherapy)
Non-Small Cell Lung Cancer (NSCLC)	In combination with nivolumab: – Administer 1 mg/kg intravenously every 6 weeks (given in combination with nivolumab 3 mg/kg every 2 weeks), until disease progression or unacceptable toxicity for up to 2 years In combination with nivolumab and platinum-doublet chemotherapy: – Administer 1 mg/kg intravenously every 6 weeks (given in combination with nivolumab 360 mg every 3 weeks and histology-based platinum-doublet chemotherapy every 3 weeks for 2 cycles), until disease progression or unacceptable toxicity for up to 2 years

Renal Cell Carcinoma (RCC), Colorectal Cancer (CRC)	Administer 1 mg/kg intravenously every 3 weeks for a total of 4 doses (given in combination with nivolumab, then follow with nivolumab monotherapy)
Malignant Pleural Mesothelioma	Initial Therapy: – Administer 1 mg/kg intravenously every 6 weeks (given in combination with nivolumab) until disease progression or unacceptable toxicity for up to 2 years Subsequent Therapy: – Administer 1 mg/kg intravenously every 6 weeks (given in combination with nivolumab) until disease progression or unacceptable toxicity for up to 2 years
** All treatments given for a maximum of 4 doses must be administered within 16 weeks of the first dose.*	

VI. Billing Code/Availability Information

HCPCS Code:

- J9228 – Injection, ipilimumab, 1 mg: 1 billable unit = 1 mg

NDC(s):

- Yervoy 200 mg/40 mL injection (single-use vial): 00003-2328-xx
- Yervoy 50 mg/10 mL injection (single-use vial): 00003-2327-xx

VII. References (STANDARD)

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Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
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
C21.8	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
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

ICD-10	ICD-10 Description
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
C43.11	Malignant melanoma of right eyelid, including canthus
C43.12	Malignant melanoma of left 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

ICD-10	ICD-10 Description
C43.8	Malignant melanoma of overlapping sites of skin
C43.9	Malignant melanoma of skin, unspecified
C45.0	Mesothelioma of pleura
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
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
C78.00	Secondary malignant neoplasm of unspecified lung
C78.01	Secondary malignant neoplasm of right lung
C78.02	Secondary malignant neoplasm of left lung
C78.6	Secondary malignant neoplasm of retroperitoneum and peritoneum
C78.7	Secondary malignant neoplasm of liver and intrahepatic bile duct
C79.31	Secondary malignant neoplasm of brain
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
Z85.820	Personal history of malignant melanoma of skin

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

Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determination (NCD), Local Coverage Determinations (LCDs), and Local Coverage Articles (LCAs) may exist and compliance with these policies is required where applicable. They can be found at: http://www.cms.gov/medicare-coverage-database/search/advanced-search.aspx. Additional indications may be covered at the discretion of the health plan.

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

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

Appendix 3 – CLINICAL LITERATURE REVIEW

OS = overall survival; PFS = progression-free survival; ORR = objective response rate; CR = complete response; PR = partial response; SD = stable disease; DoR = duration of response; TTP = time to progression; FFS = failure-free survival; EFS = event-free survival; PFR = progression free rate; RFS = recurrence-free survival; DMFS = distant metastases-free survival; DCR = disease control rate; CPS = combined positive score; SCC = squamous cell carcinoma; ASCT = autologous stem cell transplant

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 + 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	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	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**
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.

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.
Pembrolizumab + ipilimumab	2A preferred for progression after prior anti-PD-1 therapy	No	Phase 2	N/A	ORR	Subsequent therapy immediately after progression on prior single agent or combination anti-PD-1 therapy	• Combination therapy with low-dose ipilimumab with pembrolizumab demonstrated significant antitumor activity in patients with melanoma following disease progression on a PD1 antibody.
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	• Nab-paclitaxel plus carboplatin demonstrated clinical activity in both chemo-naïve and previously treated

						chemotherapy naive	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	• 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.

						after week 12) were eligible for reinduction therapy.	
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**
Ipilimumab (10 mg/kg every 3 weeks for 4 doses, then every 3 months for up to 3 years or disease recurrence or	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	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.

unacceptable toxicities)		resection, including total lymphadenec-tomy)					
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	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.

	local or regional therapy)						
Nivolumab + placebo	1 preferred (resected stage IIIA disease with SLN metastases > 1mm, stage IIIB/C disease during nodal basin ultrasound surveillance or after CLND, stage III disease following wide excision or primary tumor and TLND, following TLDN and/or complete resection of nodal recurrence) 2A 2B (if NED after initial treatment with local or	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.

	regional therapy)						

Uveal Melanoma

Distant metastatic disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
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.
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 after prior ipilimumab	• Pembrolizumab demonstrated a PFS of 18 weeks in patients with metastatic uveal melanoma. Out of 8 evaluable patients, there were 1 complete response, 2 partial response, and 1 patient with stable disease.
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.				

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 1 for poor/ intermediate risk	Yes	Phase 3 (VEG105192), open-label, double-blind, randomized, multi-center Final OS results	Placebo	PFS	First-line or after cytokine therapy	• Pazopanib demonstrated significant improvement in PFS and tumor response compared with placebo in treatment-naive and cytokine-pretreated patients with advanced and/or metastatic RCC.
Sunitinib	1 preferred for favorable risk	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.

	1 for poor/ intermediate risk						
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 + ipilimumab	2A preferred	No	Phase 1b (CheckMate-016), open-label, dose-escalation study	N/A	Safety	After one prior treatment	• Nivolumab plus ipilimumab demonstrate safety and durable response in patients with clear cell advanced or metastatic RCC, regardless of risk.
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.
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.

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 + 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.
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).
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%.
Cemiplimab-rwlc	1 preferred for PD-L1 ≥50%	Yes for TPS ≥50%	Phase 3 (EMPOWER-Lung 1), randomized, multi-center, open-label, controlled	Platinum-doublet chemotherapy	OS PFS	First-line	• Cemiplimab monotherapy significantly improved overall survival and progression-free survival compared with chemotherapy in patients with advanced non-small-cell lung cancer with PD-L1 of at least 50%.
Dabrafenib + trametinib	2A preferred	Yes (in combination with trametinib for BRAF V600E mutation-positive metastatic NSCLC)	Cohort C of Phase 2 (Study BRF113928), multi-center, open-label	N/A	ORR	First-line	• Dabrafenib plus trametinib demonstrated a clinically meaningful antitumor activity with an ORR of 64% and a manageable safety profile in patients with previously untreated BRAFV600E-mutant NSCLC.

Dabrafenib	2A	No	Cohort A of Phase 2 (Study BRF113928), 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 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%).
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 V600E-mutation positive or NTRK gene fusion positive tumors)	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
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),	Carboplatin or cisplatin + pemetrexed	OS	First-line	• IMpower110 met the primary OS endpoint with statistically significant and clinically meaningful

			randomized, open-label	(non-squamous) or gemcitabine (squamous)			improvement as first-line therapy in patients with TC ≥50% or IC ≥10%.
Cemiplimab-rwlc	1 preferred for PD-L1 ≥50%	Yes for TPS ≥50%	Phase 3 (EMPOWER-Lung 1), randomized, multi-center, open-label, controlled	Platinum-doublet chemotherapy	OS PFS	First-line	• Cemiplimab monotherapy significantly improved overall survival and progression-free survival compared with chemotherapy in patients with advanced non-small-cell lung cancer with PD-L1 of at least 50%.
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, SCOUT, and NAVIGATE)	N/A	ORR	All lines of therapy (98% had received prior treatment)	• Larotrectinib demonstrated an ORR of 75% in patents with NTRK gene fusion positive disease across a range of solid tumors.
Entrectinib	2A preferred	Yes	Phase 1/2 (STARTRK-2, STARTRK-1 and ALKA-372-001)	N/A	ORR DOR	TRK inhibitor-naïve	• Entrectinib induced clinically meaningful responses in patients with NTRK-FP solid tumors, including those with NSCLC (ORR 70%).

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) 2A (for subsequent progression)	Yes	Phase 3 (CheckMate 057), randomized, open-label	Docetaxel	OS	Subsequent	• Among patients with advanced nonsquamous NSCLC that had progressed during or after platinum-based chemotherapy, overall survival was longer with nivolumab than with docetaxel
Pembrolizumab (2 mg/kg vs. 10 mg/kg)	1 preferred (first progression)	Yes (PD-L1 ≥1% with disease progression on	Phase 2/3 (KEYNOTE-010),	Docetaxel	OS PFS	Previously treated	• Pembrolizumab prolongs overall survival in patients with previously treated, PD-L1-positive, advanced non-small-cell lung cancer.

	2A (subsequent progression)	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)	randomized, multicenter, open-label, active-controlled trial				
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 on or intolerant to crizotinib	Phase 2 (ALTA), randomized	N/A	ORR	Crizotinib-refractory	• Brigatinib (180 mg once daily with lead-in) demonstrated a longer PFS and ORR 56% in patients with crizotinib refractory ALK-positive NSCLC.
Ceritinib	2A (ALK-positive, after progression on crizotinib)	Yes for ALK-positive mNSCLC	Phase 3 (ASCEND-5), randomized, controlled, open-label	Pemetrexed or docetaxel	PFS	Progressed following crizotinib and platinum-based doublet chemotherapy	• After failure of crizotinib, ceritinib significantly improved PFS compared to single-agent chemotherapy

Malignant Pleural Mesothelioma

First-line therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Nivolumab + ipilimumab	1 preferred	Yes	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		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.

Colorectal Cancer (CRC)

Neoadjuvant therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Nivolumab + ipilimumab	2A	No	No clinical literature evidence to support use.				
Subsequent therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Nivolumab + ipilimumab	2A	No	Phase 2 (CheckMate-142) Two-year clinical update	N/A	ORR	First-line (prior adjuvant or neoadjuvant therapy allowed)	• Nivolumab plus ipilimumab demonstrated an ORR of 69% as first-line treatment of dMMR/MSI-H mCRC.
Pembrolizumab	2A	Yes	Phase 3 (KEYNOTE-177), randomized, open-label	Standard of care chemotherapy (FOLFOX or FOLFIRI ± bevacizumab or cetuximab)	PFS OS	First-line	• Pembrolizumab demonstrated a clinically meaningful and statistically significant 40% reduction in the risk of disease progression compared to chemotherapy in patients with MSI-H or dMMR CRC.
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.
Pembrolizumab	2A	Yes	Phase 2 (KEYNOTE-016)	N/A	ORR 20-week PFS	CRC: after at least 2 prior cancer therapy regimens Non-CRC: after at least 1 prior cancer therapy	• This study showed that mismatch-repair status predicted clinical benefit of immune checkpoint blockade with pembrolizumab (ORR 40% and 20-week PFs 78%).
Pembrolizumab	2A	Yes	Phase 2 (KEYNOTE-164)	N/A	ORR	Cohort A: after prior fluoropyrimidine, oxaliplatin, and irinotecan Cohort B: after prior fluoropyrimidine + oxaliplatin or fluoropyrimidine + irinotecan +/- anti-VEGF/EGFR monoclonal antibody (mAb)	• Pembrolizumab demonstrated anti-tumor efficacy in patients with previously treated dMMR metastatic colorectal cancer with an ORR of 33%.

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	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.

		treatment options					

Hepatocellular Carcinoma (HCC)

Subsequent therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
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).
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.

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,	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,

			double-blind, multi-center				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.				