Bevacizumab:
Avastin®; Mvasi™; Zirabev™
(Intravenous)

ONCOLOGY

-E-

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I. Length of Authorization [6]

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

- For CNS cancers (symptom management), coverage will be provided for 12 weeks and may NOT be renewed.
- For initial/adjuvant treatment of ovarian cancer, coverage will be provided for up to a maximum of 22 cycles (66 weeks).

II. Dosing Limits

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

- 100 mg/4 mL vial: 3 vials 21 days
- 400 mg/16 mL vial: 4 vials per 21 days

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

Oncology indications (J9035/Q5107/Q5118):

- Small Bowel Adenocarcinoma:
  - 60 billable units per 14 days
- CRC, CNS & RCC:
  - 120 billable units per 14 days
- All other indications:
  - 170 billable units per 21 days
  - 120 billable units per 14 days

III. Initial Approval Criteria [1-3]

Coverage is provided in the following conditions:

Patient must have a contraindication or intolerance to all of the following prior to consideration of Avastin® (J9035): bevacizumab-awwb (Mvasi™ [Q5107]) and bevacizumab-bvzr (Zirabev™ [Q5118]); **AND**

- Patient is at least 18 years of age; **AND**

Universal Criteria [1]

- Patient has no recent history of hemoptysis (i.e., the presence of ≥2.5 mL of blood in sputum) OR any grade 3-4 hemorrhage; **AND**
- Patient must not have had a surgical procedure within the preceding 28 days or have a surgical wound that has not fully healed; **AND**

Colorectal Cancer (CRC) † ‡ [1-4,17-22]

- Will not be used as part of adjuvant treatment; **AND**
- Will not be used in combination with an anti-EGFR agent (e.g., panitumumab or cetuximab); **AND**
  - Patient has metastatic, unresectable, or advanced disease; **AND**
    - Used as first-line or subsequent therapy in combination with a fluoropyrimidine- (e.g., 5-fluorouracil/5-FU or capecitabine) or irinotecan- based regimen; **OR**
  - Used in combination with a fluoropyrimidine-irinotecan or fluoropyrimidine-oxaliplatin-based regimen (if not used first line) as second-line therapy for advanced or metastatic disease that has progressed on a first-line bevacizumab containing regimen; **OR**
  - Used in combination with trifluridine and tipiracil as subsequent therapy for advanced or metastatic disease after progression on all available regimens

Non-Squamous Non-Small Cell Lung Cancer (NSCLC) † [1-4,10,12,13,23,24,41e-43e,47e,172e]

- Used as first-line therapy for recurrent, locally advanced, unresectable, or metastatic disease in combination with carboplatin and paclitaxel †; **OR**
- Used for recurrent, advanced, or metastatic disease (excluding locoregional recurrence or symptomatic local disease with no 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:
      - EGFR, ALK, ROS1, BRAF, NTRK1/2/3, MET exon 14 skipping mutation, and RET rearrangement negative* tumors and PD-L1 < 1% in patients with PS ≤ 1; **OR**
      - EGFR, ALK, ROS1, BRAF, NTRK1/2/3, MET exon 14 skipping mutation, and RET rearrangement negative tumors* and PD-L1 ≥ 1% in patients with PS ≤ 2; **OR**
      - BRAF V600E-mutation, NTRK1/2/3 gene fusion, MET exon 14 skipping mutation, or RET rearrangement positive tumors in patients with PS ≤ 1; **AND**
    - Used in combination with:

        - Atezolizumab, carboplatin and paclitaxel; **OR**
    - Used as subsequent therapy in patients with PS ≤ 1; **AND**
        - Used for one of the following:
            - EGFR, ALK, or ROS1 positive tumors and prior targeted therapy**§**; **OR**
            - BRAF V600E-mutation, NTRK1/2/3 gene fusion, MET exon 14 skipping mutation, or RET rearrangement positive tumors; **OR**
            - PD-L1 expression-positive (PD-L1 ≥ 1%) tumors that are EGFR, ALK, ROS1, BRAF, NTRK1/2/3, MET exon 14 skipping mutation, and RET negative***** with prior PD-1/PD-L1 inhibitor therapy but no prior platinum-doublet chemotherapy; **AND**
        - Used in combination with:
            - Carboplatin and paclitaxel; **OR**
            - Atezolizumab, carboplatin and paclitaxel *(excluding use in patients who have received prior PD-1/PD-L1 inhibitor therapy)*; **OR**
    - Used as continuation maintenance therapy (*bevacizumab must have been included in patient's first-line chemotherapy regimen*) in patients with PS ≤ 2 who achieved tumor response or stable disease after first-line systemic therapy; **AND**
        - Used as a single agent; **OR**
        - Used in combination with atezolizumab following a first-line atezolizumab/carboplatin/paclitaxel/bevacizumab regimen; **OR**
    - Used in combination with erlotinib for sensitizing EGFR mutation positive disease; **AND**
        - Used as first-line therapy; **OR**
        - Used as continuation of therapy following disease progression on erlotinib with bevacizumab for asymptomatic disease, symptomatic brain lesions, or isolated symptomatic systemic lesions

> ** 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.*

Cervical Cancer † ‡ [1-4]

- Patient has persistent, recurrent, or metastatic disease; **AND**
- Used as first-line therapy in combination with paclitaxel AND either cisplatin, carboplatin, or topotecan

Renal Cell Carcinoma (RCC) † [1-4,27,65e,68e,74e-78e]

- Used in combination with interferon alfa for metastatic disease as first-line therapy for clear cell histology **†**; **OR**
- Patient has metastatic or relapsed disease; **AND**
    - Used in combination with everolimus as first-line therapy in patients with non-clear cell histology **‡**; **OR**

- Used in combination with erlotinib as first- or second-line therapy in patients with non-clear cell histology advanced papillary disease including hereditary leiomyomatosis and renal cell cancer (HLRCC) ‡

Central Nervous System (CNS) Cancer [1-4,6,25,26,81e,90e,97e,151e,153e]

- Used for symptom management related to radiation necrosis, poorly controlled vasogenic edema, or mass effect as single-agent short-course therapy; **AND**
  - Patient has a diagnosis of one of the following other CNS cancers ‡:
    - Infiltrative Supratentorial Astrocytoma/Oligodendroglioma (Low-Grade, WHO Grade II); **OR**
    - Primary CNS Lymphoma; **OR**
    - Meningiomas; **OR**
    - Brain or Spine metastases; **OR**
    - Medulloblastoma; **OR**
    - Glioblastoma or Anaplastic Gliomas; **OR**
    - Intracranial or Spinal Ependymoma *(excluding subependymoma)*; **OR**
- Used as a single agent OR in combination with lomustine or temozolomide in patients with recurrent Glioblastomas † ‡

Ovarian Cancer † ‡ Φ [1,4,11,29-32,103e,110e,116e,120e,166e]

- Patient has malignant stage II-IV sex cord-stromal tumors ‡; **AND**
  - Used as single agent therapy for clinically relapsed disease; **OR**
- Patient has epithelial ovarian or fallopian tube or primary peritoneal cancer †; **AND**
  - Patient has persistent or recurrent disease; **AND**
    - Bevacizumab has not been used previously; **AND**
    - Patient is not experiencing an immediate biochemical relapse (i.e., rising CA-125 without radiographic evidence of disease); **AND**
      - Patient has platinum sensitive disease; **AND**
        - Used as a single agent; **OR**
        - Used in combination with niraparib; **OR**
        - Used in combination with carboplatin AND PEGylated liposomal-doxorubicin; **OR**
      - Patient has platinum resistant disease; **AND**
        - Used as a single agent; **OR**
        - Used in combination with one of the following: oral cyclophosphamide, PEGylated liposomal doxorubicin, paclitaxel, or topotecan †; **OR**
  - Used for rising CA-125 levels or clinical relapse in patients who have received no prior chemotherapy in combination with paclitaxel and carboplatin; **OR**
  - Used as maintenance therapy; **AND**

        - Used as a single agent *(for BRCA1/2 wild-type or unknown only)* or in combination with olaparib following primary therapy including bevacizumab; **OR**
        - Used as single agent following recurrence therapy with chemotherapy plus bevacizumab for platinum-sensitive disease; **OR**
        - Used in combination with paclitaxel and carboplatin for stable disease following neoadjuvant therapy as continued maintenance therapy; **OR**
    - Used as neoadjuvant therapy for endometrioid or serous histology in combination with paclitaxel and carboplatin; **AND**
        - Patient is a poor surgical candidate or has a low likelihood of optimal cytoreduction; **OR**
    - Used as adjuvant therapy in combination with paclitaxel and carboplatin; **AND**
        - Patient has pathologic stage II-IV disease; **OR**
        - Patient is a poor surgical candidate or has a low likelihood of optimal cytoreduction; **AND**
            - Patient has endometrioid or serous histology; **AND**
            - Used after interval debulking surgery (IDS) in patients with a response or stable disease to neoadjuvant therapy

Soft Tissue Sarcoma ‡ [4,34,122e,126e]

- Used as a single agent for angiosarcoma

Endometrial Carcinoma (Uterine Neoplasms) ‡ [4,35,133e-136e]

- Used as single agent therapy for disease that has progressed on prior cytotoxic chemotherapy; **OR**
- Used in combination with carboplatin and paclitaxel for advanced and recurrent disease

Malignant Pleural Mesothelioma (MPM)* ‡ [4,37,137e]

- Patient has unresectable disease OR clinical stage IIIB or IV disease, sarcomatoid, or medically inoperable tumors; **AND**
- Used as first-line therapy in combination with pemetrexed and cisplatin or carboplatin as initial therapy, followed by single-agent maintenance bevacizumab

**peritoneal, pericardial, and tunica vaginalis testis mesothelioma will be evaluated on a case-by-case basis*

Small Bowel Adenocarcinoma ‡ [4,16,158e]

- Used as initial therapy; **AND**
- Patient has advanced or metastatic disease; **AND**
- Used in combination with CapeOX (capecitabine plus oxaliplatin)

Hepatocellular Carcinoma (HCC) † ‡ Φ [1-4,14,15,164e]

- Used as first-line therapy in combination with atezolizumab; **AND**
- Patient has Child-Pugh Class A disease; **AND**
- Patient has locally advanced, unresectable, inoperable, or metastatic disease

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

† FDA-labeled 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 [1-4]

Coverage can be renewed based upon 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**

- Disease response with treatment as defined by stabilization of disease or decrease in size of tumor or tumor spread; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: gastrointestinal perforations and fistulae, surgical/wound healing complications, hemorrhage, arterial and venous thromboembolic events (ATE & VTE), uncontrolled hypertension, posterior reversible encephalopathy syndrome (PRES), nephrotic syndrome, proteinuria, severe infusion reactions, ovarian failure, congestive heart failure (CHF), etc.; **AND**

CNS Cancers – symptom management (short-course therapy):

- May NOT be renewed

Colorectal Cancer (after first-line bevacizumab-containing regimen):

- *Refer to Section III for criteria*

Malignant Pleural Mesothelioma (maintenance therapy):

- *Refer to Section III for criteria*

Ovarian Cancer (initial/adjuvant therapy):

- May NOT exceed 22 cycles (66 weeks) of therapy

Ovarian Cancer (maintenance therapy):

- *Refer to Section III for criteria*

Non-Squamous Non-Small Cell Lung Cancer (continuation therapy in combination with erlotinib):

- *Refer to* Section *III for criteria*

V. Dosage/Administration [1-3,5,6,16,33,36-38]

Indication	Dose
CRC	Administer 5 to 10 mg/kg intravenously every 2 weeks **OR** 7.5 mg/kg intravenously every 3 weeks until disease progression or unacceptable toxicity.
Small Bowel Adenocarcinoma	Administer 5 mg/kg intravenously every 2 weeks **OR** 7.5 mg/kg intravenously every 3 weeks until disease progression or unacceptable toxicity.
NSCLC & Cervical Cancer	Administer 15 mg/kg intravenously every 3 weeks until disease progression or unacceptable toxicity.
CNS Cancers	–For disease treatment: Administer 10 mg/kg intravenously every 2 weeks until disease progression or unacceptable toxicity. –For symptom management: Administer 5 to 10 mg/kg intravenously every 2 weeks up to 12 weeks duration.
RCC	Administer 10 mg/kg intravenously every 2 weeks until disease progression or unacceptable toxicity.
MPM	Administer 15 mg/kg intravenously every 3 weeks in combination with chemotherapy for up to 6 cycles. May follow with maintenance therapy with single-agent bevacizumab 15 mg/kg intravenously every 3 weeks, until disease progression or unacceptable toxicity.

Ovarian Cancer	**Initial/Adjuvant Therapy** Administer 15 mg/kg intravenously every 3 weeks in combination with carboplatin and paclitaxel for up to 6 cycles, followed by single agent bevacizumab 15 mg/kg every 3 weeks for up to a total of 22 cycles or until disease progression or unacceptable toxicity, whichever occurs earlier. **Persistent/Recurrent Disease** Platinum-sensitive disease: Administer 15 mg/kg intravenously every 3 weeks until disease progression or unacceptable toxicity. Platinum-resistant disease: Administer 10 mg/kg intravenously every 2 weeks **OR** 15 mg/kg every 3 weeks until disease progression or unacceptable toxicity. **All Other Treatment Settings** Administer 5 to 10 mg/kg intravenously every 2 weeks **OR** 7.5 to 15 mg/kg intravenously every 3 weeks until disease progression or unacceptable toxicity.
HCC	Administer 15 mg/kg intravenously every 3 weeks until disease progression or unacceptable toxicity.
All Other Oncology Indications	Administer 5 to 10 mg/kg intravenously every 2 weeks **OR** 7.5 to 15 mg/kg intravenously every 3 weeks until disease progression or unacceptable toxicity.

VI. Billing Code/Availability Information

HCPCS Code:

- J9035 – Injection, bevacizumab, 10 mg; 1 billable unit = 10 mg
- Q5107 – Injection, bevacizumab-awwb, biosimilar, (mvasi), 10 mg: 1 billable unit = 10 mg
- Q5118 – Injection, bevacizumab-bvzr, biosimilar, (zirabev), 10 mg; 1 billable unit = 10 mg

NDC(s):

- Avastin single-use vial, 100 mg/4 mL solution for injection: 50242-0060-xx
- Avastin single-use vial, 400 mg/16 mL solution for injection: 50242-0061-xx
- Mvasi single-use vial, 100 mg/4 mL solution for injection: 55513-0206-xx
- Mvasi single-use vial, 400 mg/16 mL solution for injection: 55513-0207-xx
- Zirabev single-use vial, 100 mg/4 mL solution for injection: 00069-0315-xx
- Zirabev single-use vial, 400 mg/16 mL solution for injection: 00069-0342-xx

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Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
C17.0	Malignant neoplasm duodenum

ICD-10	ICD-10 Description
C17.1	Malignant neoplasm jejunum
C17.2	Malignant neoplasm ileum
C17.3	Meckel's diverticulum, malignant
C17.8	Malignant neoplasm of overlapping sites of small intestines
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 large intestines
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
C22.3	Angiosarcoma of the liver
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
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 or 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

ICD-10	ICD-10 Description
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
C45.0	Mesothelioma of pleura
C45.1	Mesothelioma of peritoneum
C48.0	Malignant neoplasm of retroperitoneum
C48.1	Malignant neoplasm of specified parts of peritoneum
C48.2	Malignant neoplasm of peritoneum, unspecified
C48.8	Malignant neoplasm of overlapping sites of retroperitoneum and peritoneum
C49.0	Malignant neoplasm of connective and soft tissue of head, face and neck
C49.10	Malignant neoplasm of connective and soft tissue of unspecified upper limb, including shoulder
C49.11	Malignant neoplasm of connective and soft tissue of right upper limb including shoulder
C49.12	Malignant neoplasm of connective and soft tissue of left upper limb, including shoulder
C49.20	Malignant neoplasm of connective and soft tissue of unspecified lower limb, including hip
C49.21	Malignant neoplasm of connective and soft tissue of right lower limb, including hip
C49.22	Malignant neoplasm of connective and soft tissue of left lower limb, including hip
C49.3	Malignant neoplasm of connective and soft tissue of thorax
C49.4	Malignant neoplasm of connective and soft tissue of abdomen
C49.5	Malignant neoplasm of connective and soft tissue of pelvis
C49.6	Malignant neoplasm of connective and soft tissue of trunk, unspecified
C49.8	Malignant neoplasm of overlapping sites of connective and soft tissue
C49.9	Malignant neoplasm of connective and soft tissue, unspecified
C53.0	Malignant neoplasm of endocervix
C53.1	Malignant neoplasm of exocervix
C53.8	Malignant neoplasm of overlapping sites of cervix uteri
C53.9	Malignant neoplasm of cervix uteri, unspecified
C54.0	Malignant neoplasm of isthmus uteri
C54.1	Malignant neoplasm of endometrium
C54.2	Malignant neoplasm of myometrium
C54.3	Malignant neoplasm of fundus uteri
C54.8	Malignant neoplasm of overlapping sites of corpus uteri
C54.9	Malignant neoplasm of corpus uteri, unspecified
C55	Malignant neoplasm of uterus, part unspecified
C56.1	Malignant neoplasm of right ovary
C56.2	Malignant neoplasm of left ovary
C56.9	Malignant neoplasm of unspecified ovary
C57.00	Malignant neoplasm of unspecified fallopian tube

ICD-10	ICD-10 Description
C57.01	Malignant neoplasm of right fallopian tube
C57.02	Malignant neoplasm of left fallopian tube
C57.10	Malignant neoplasm of unspecified broad ligament
C57.11	Malignant neoplasm of right broad ligament
C57.12	Malignant neoplasm of left broad ligament
C57.20	Malignant neoplasm of unspecified round ligament
C57.21	Malignant neoplasm of right round ligament
C57.22	Malignant neoplasm of left round ligament
C57.3	Malignant neoplasm of parametrium
C57.4	Malignant neoplasm of uterine adnexa, unspecified
C57.7	Malignant neoplasm of other specified female genital organs
C57.8	Malignant neoplasm of overlapping sites of female genital organs
C57.9	Malignant neoplasm of female genital organ, unspecified
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
C70.9	Malignant neoplasm of meninges, unspecified
C71.0	Malignant neoplasm of cerebrum, except lobes and ventricles
C71.1	Malignant neoplasm of frontal lobe
C71.2	Malignant neoplasm of temporal lobe
C71.3	Malignant neoplasm of parietal lobe
C71.4	Malignant neoplasm of occipital lobe
C71.5	Malignant neoplasm of cerebral ventricle
C71.6	Malignant neoplasm of cerebellum
C71.7	Malignant neoplasm of brain stem
C71.8	Malignant neoplasm of overlapping sites of brain
C71.9	Malignant neoplasm of brain, unspecified
C72.0	Malignant neoplasm of spinal cord
C72.9	Malignant neoplasm of central nervous system, unspecified
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

ICD-10	ICD-10 Description
C79.31	Secondary malignant neoplasm of brain
C83.30	Diffuse large B-cell lymphoma unspecified site
C83.39	Diffuse large B-cell lymphoma extranodal and solid organ sites
C83.80	Other non-follicular lymphoma unspecified site
C83.89	Other non-follicular lymphoma extranodal and solid organ sites
C85.89	Other specified types of non-Hodgkin lymphoma, extranodal and solid organ sites
D43.0	Neoplasm of uncertain behavior of brain, supratentorial
D43.1	Neoplasm of uncertain behavior of brain, infratentorial
D43.2	Neoplasm of uncertain behavior of brain, unspecified
D43.4	Neoplasm of uncertain behavior of spinal cord
I67.89	Other cerebrovascular disease
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
Z85.43	Personal history of malignant neoplasm of ovary
Z85.831	Personal history of malignant neoplasm of soft tissue
Z85.841	Personal history of malignant neoplasm of brain

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/LCA Document (s):** A52370
https://www.cms.gov/medicare-coverage-database/search/article-date-search.aspx?DocID=A52370&bc=gAAAAAAAAAAAAA==	

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)

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
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; DoR = duration of response; TTP = time to progression; FFS = failure-free survival; EFS = event-free survival; PFR = progression free rate; CBR = clinical benefit rate; SCC = squamous cell carcinoma; FOLFOX = 5-FU/leucovorin/oxaliplatin; FOLFIRI = 5-FU/leucovorin/irinotecan; CapeOX = capecitabine/oxaliplatin

Colorectal Cancer (CRC)

First-line therapy of metastatic disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bevacizumab (bev) + irinotecan + bolus 5FU+ leucovorin (IFL)	2A	Yes	Phase 3 (Study AVF2107g), randomized, double-blind, active-controlled	IFL + placebo	OS	First-line	• The addition of bevacizumab to fluorouracil-based combination chemotherapy results in statistically significant improvement in survival (4.7 month increase in median OS) among patients with metastatic colorectal cancer
Bevacizumab + FOLFOX	2A	Yes	Phase 2 (TREE study), randomized, open-label	Bevacizumab + bFOL (bolus FU, LV, oxaliplatin) vs. bevacizumab + CapeOX	Incidence of grade 3/4 AEs	First-line	• The addition of bevacizumab to oxaliplatin and fluoropyrimidine regimens is well tolerated as first-line treatment of mCRC and does not markedly change overall toxicity. • First-line oxaliplatin and fluoropyrimidine-based therapy plus bevacizumab resulted in a median OS of approximately 2 years.
Bevacizumab + FOLFOX or XELOX	2A	Yes	Phase 3 (NO16966), randomized	Placebo + FOLFOX or XELOX	PFS	First-line	• The addition of bevacizumab to oxaliplatin-based chemotherapy

							significantly improved PFS in this first-line trial in patients with mCRC • Overall survival differences did not reach statistical significance, and response rate was not improved by the addition of bevacizumab.
Bevacizumab + FOLFOXIRI	2A	Yes	Phase 3 (TRIBE), randomized, open-label, multi-center Updated analysis	Bevacizumab + FOLFIRI	PFS	First-line	• FOLFOXIRI plus bevacizumab, as compared with FOLFIRI plus bevacizumab, improved the outcome in patients with metastatic colorectal cancer and increased the incidence of some adverse events
Bevacizumab + capecitabine			Phase 3 (AVEX), open-label, randomized	Capecitabine	PFS	First-line	• The combination of bevacizumab and capecitabine demonstrated a significant improvement in PFS and was well-tolerated in elderly patients with metastatic colorectal cancer
Bevacizumab + FU + LV			Phase 2, randomized	FU + LV + placebo	OS	First-line	• Addition of bevacizumab to FU/LV as first-line therapy in CRC patients who were not considered optimal candidates for first-line irinotecan treatment provided clinically significant patient benefit, including statistically significant improvement in progression-free survival.
Cetuximab + FOLFIRI	2A (for KRAS/ NRAS WT and left-sided tumors only)	Yes	Phase 3 (CRYSTAL), randomized, open-label, multi-center	FOLFIRI	PFS	First-line	• First-line treatment with cetuximab plus FOLFIRI, as compared with FOLFIRI alone, reduced the risk of progression of metastatic colorectal cancer. The benefit of cetuximab was

			Updated analysis				limited to patients with KRAS wild-type tumors.
Cetuximab + FOLFOX	2A (for KRAS/ NRAS WT and left-sided tumors only)		Phase 3 (TAILOR), open-label, randomized	FOLFOX	PFS	First-line	• Combination of FOLFOX with cetuximab is effective in first-line treatment of patients with RAS wild-type mCRC with a benefit in both PFS and OS.
Panitumumab + FOLFOX	2A (for KRAS/ NRAS WT and left-sided tumors only)	Yes	Phase 3 (PRIME), randomized, open-label Final results	FOLFOX	PFS	First-line	• Additional RAS mutations predicted a lack of response in patients who received panitumumab-FOLFOX4. In patients who had metastatic colorectal cancer without RAS mutations, improvements in overall survival were observed with panitumumab-FOLFOX4 therapy
Panitumumab+ FOLFIRI	2A (for KRAS/ NRAS WT and left-sided tumors only)	No	Phase 2, single-arm	N/A	---------	First-line	• A favorable efficacy (ORR 56%) was observed in patients with KRAS wild-type CRC receiving first-line panitumumab plus FOLFIRI treatment.
Bevacizumab + FOLFIRI	2A	Yes	Phase 3 (FIRE-3), randomized, open-label Primary tumor location analysis	Cetuximab + FOLFIRI	ORR	First-line	• The proportion of patients who achieved an objective response did not significantly differ between the FOLFIRI plus cetuximab and FOLFIRI plus bevacizumab. A longer association in OS with FOLFIRI plus cetuximab was demonstrated for patients with KRAS exon 2 wild-type metastatic colorectal cancer. • More benefit was shown for cetuximab in left-sided tumors than bevacizumab.

Bevacizumab + FOLFOX or FOLFIRI	2A	Yes	Phase 3 (CALGB/ SWOG), randomized Retrospective re-analysis – Impact of primary tumor location	Cetuximab + FOLFOX or FOLFIRI	OS	First-line	• Among patients with KRAS WT untreated advanced or metastatic colorectal cancer, there was no significant difference in overall survival between the addition of cetuximab vs bevacizumab to chemotherapy as initial biologic treatment. • In KRAS wild type mCRC, patients with left-sided primary tumor have superior OS and PFS versus patients with right-sided primary tumor.
Panitumumab + FOLFOX	2A (for KRAS/ NRAS WT and left-sided tumors only)	Yes	Phase 2 (PEAK), randomized, multi-center	Bevacizumab + FOLFOX	PFS	First-line	• PFS was similar and OS was improved with panitumumab relative to bevacizumab when combined with FOLFOX in patients with wild-type KRAS tumors.
Bevacizumab-containing regimen	2A	Yes	Retrospective meta-analysis of FIRE-3, CALGB/ SWOG 80405, & PEAK	Cetuximab or panitumumab-containing regimens	---------	First-line	• RAS wild-type left-sided CRC had a significantly greater survival benefit from anti-EGFR treatment compared with anti-VEGF treatment when added to standard chemo • Bevacizumab was associated with a longer survival in patients with right-sided CRC
After first-line bevacizumab-containing regimen in metastatic disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bevacizumab (bev) + fluoropyrimidine-	2A	Yes	Phase 3 (TML/ML18147 study),	Fluoropyrimidine-based chemotherapy	OS	Previous treatment with bev +	• Maintenance of VEGF inhibition with bevacizumab plus standard second-line chemotherapy beyond disease progression has clinical benefits in OS

based chemotherapy including either irinotecan or oxaliplatin			prospective, randomized, open-label, multinational, controlled	including either irinotecan or oxaliplatin		fluoropyrimidine and either oxaliplatin or irinotecan	and PFS in patients with metastatic colorectal cancer. Treatment effects were independent of KRAS mutation status.
Second-line therapy for metastatic disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bevacizumab + 5-fluorouracil (5-FU) + leucovorin + oxaliplatin (FOLFOX4)	2A (preferred after previous oxaliplatin- or fluoropyrimidine-based therapy without irinotecan or oxaliplatin)	Yes	Phase 3 (Study E3200), open-label, randomized, active-controlled, multicenter	5-fluorouracil (5-FU) + leucovorin + oxaliplatin (FOLFOX4)	OS	Second-line	• The addition of bevacizumab to oxaliplatin, fluorouracil, and leucovorin improves survival duration for patients with previously treated metastatic colorectal cancer
Bevacizumab + FOLFIRI	2A (preferred after previous oxaliplatin- or fluoropyrimidine-based therapy without irinotecan or oxaliplatin)	Yes	Phase 2 (SPIRITT), randomized, multi-center	Panitumumab + FOLFIRI	PFS	Second-line after oxaliplatin-based therapy plus bevacizumab	• Panitumumab or bevacizumab with FOLFIRI as second-line treatment had efficacy similar in patients whose disease progressed during oxaliplatin-based chemotherapy with bevacizumab
Bevacizumab + TAS-102 (trifluridine + tipiracil)	2A	No	Phase 2, randomized, open-label	TAS-102 (trifluridine + tipiracil)	PFS	Refractory or intolerant to a fluoropyrimidine, irinotecan, oxaliplatin, and cetuximab or	• In patients with chemorefractory metastatic colorectal cancer, TAS-102 plus bevacizumab, as compared with TAS-102 monotherapy, was associated with a significant and clinically relevant

						panitumumab (only for RAS wild-type)	improvement in progression-free survival with tolerable toxicity.
Panitumumab	2A	No	Phase 3, open-label, randomized Retrospective analysis	Best supportive care (BSC)	PFS	After disease progression on oxaliplatin/ irinotecan-based chemotherapy	• Panitumumab monotherapy efficacy in mCRC is confined to patients with WT KRAS tumors
Panitumumab	2A	Yes	Phase 3, randomized	Best supportive care (BSC)	OS	After disease progression on oxaliplatin/ irinotecan-based chemotherapy	• Panitumumab significantly improved OS in wild-type KRAS exon 2 mCRC.
Panitumumab + FOLFIRI	2A	Yes	Phase 3 (Study 181), randomized	FOLFIRI	PFS OS	Second-line	• Panitumumab plus FOLFIRI significantly improved PFS, however the improvement in OS was nonsignificant
Cetuximab + irinotecan	2A	Yes	Phase 3 (EPIC), multi-center, open-label	Irinotecan	OS	After fluoropyrimidine and oxaliplatin	• Cetuximab and irinotecan improved PFS and ORR versus irinotecan alone. OS was similar between study groups
Panitumumab	2A	No	Phase 3 (ASPECCT), randomized, multi-center, open-label,	Cetuximab	Non-inferiority OS	Chemo-refractory	• Panitumumab is non-inferior to cetuximab. These agents provide similar overall survival benefit in patients with KRAS wild type mCRC.

			non-inferiority				
Ziv-Aflibercept+ FOLFIRI	2A (after regimen NOT containing irinotecan)	Yes	Phase 3 (VELOUR), randomized Subgroup analysis	FOLFIRI + placebo	OS	Second-line after oxaliplatin-based regimen	• Aflibercept in combination with FOLFIRI conferred a statistically significant survival benefit over FOLFIRI combined with placebo in patients with mCRC previously treated with oxaliplatin • Benefit in OS was also shown in patients with prior bevacizumab treatment
Ramucirumab +FOLFIRI	2A (after regimen NOT containing irinotecan)	Yes	Phase 3 (RAISE), randomized, double-blind, multi-center	FOLFIRI + placebo	OS	After first-line fluoro + oxali + bev	• Ramucirumab plus FOLFIRI significantly improved overall survival compared with placebo plus FOLFIRI as second-line treatment for patients with metastatic colorectal carcinoma
Pembrolizumab	2A	Yes	Phase 2	N/A	ORR PFS rate	After 2-4 previous therapies	• Mismatch-repair status predicted clinical benefit of immune checkpoint blockade with pembrolizumab in patients with CRC
Nivolumab +/- ipilimumab	2A	Yes	Phase 2 (CheckMate-142), open-label, multi-center	N/A	ORR	Second-line or later	• Nivolumab provided durable responses and disease control in pre-treated patients with dMMR/MSI-H metastatic colorectal cancer
Bevacizumab + FOLFIRI or FOLFOX	2A	Yes	Phase 2 (PRODIGE 18), randomized	Erbitux + FOLFIRI or FOLFOX	PFS	Second-line after Avastin chemotherapy	• In wtKRAS mCRC patients progressing after bevacizumab plus chemotherapy, continuation beyond progression with bevacizumab and crossover chemotherapy is associated with a numerically higher but not statistically significant median PFS and OS

							compared to cetuximab plus chemotherapy.

Non-Squamous Non-Small Cell Lung Cancer (NSCLC)

First-Line Therapy of Recurrent, Advanced, or Metastatic Disease - EGFR, ALK negative or unknown, PD-L1 ≥ 50%							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pembrolizumab	1 preferred	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%.
First-Line Therapy of Recurrent, Advanced, or Metastatic Disease							

Regimen	NCCN Category	FDA Approved	Trial Design	Comparator	Primary End-Point	Line of Therapy	Conclusion
Bevacizumab + carboplatin + paclitaxel, followed by maintenance therapy with bevacizumab	1 (for adeno-carcinoma only; PS 0-1)	Yes	Phase 2/3 (ECOG 4599), randomized	Carboplatin + paclitaxel	OS	First-line	• The addition of bevacizumab to paclitaxel plus carboplatin in the treatment of selected patients with non-small-cell lung cancer has a significant survival benefit with the risk of increased treatment-related deaths
Atezolizumab + carboplatin + paclitaxel + bevacizumab (ABCP), followed by maintenance 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) vs. bevacizumab + carboplatin + paclitaxel (BCP)	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
Pembrolizumab + carboplatin (or cisplatin) + pemetrexed. followed by pembrolizumab + pemetrexed maintenance therapy for up to 35 total cycles	1 preferred (for adeno-carcinoma only; PS 0-1)	Yes	Phase 3 (KEYNOTE-189), double-blind, randomized (2:1)	Carboplatin (or cisplatin) + pemetrexed + placebo	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

Carboplatin + docetaxel (DCb) or Cisplatin + docetaxel (DC)	1 (for PS 0-1) 2A (for PS 2)	No	Phase 3 (TAX 326), randomized, multinational	Cisplatin + vinorelbine (VC)	----------	First-line	• DC resulted in a more favorable ORR and OS rate than VC. Both DC and DCb were better tolerated and provided patients with consistently improved QoL compared with VC. These findings demonstrate that a docetaxel plus platinum combination is an effective treatment option with a favorable therapeutic index for first-line treatment of advanced or metastatic /NSCLC.
Carboplatin + paclitaxel (TC)	1 (for PS 0-1) 2A (for PS 2)	No	Phase 3, randomized	Cisplatin + irinotecan (IP) vs. cisplatin + gemcitabine (GP) vs. cisplatin + vinorelbine (NP)	OS	First-line	• The four regimens have similar efficacy and different toxicity profiles, and they can be used to treat advanced NSCLC patients.
Cisplatin + etoposide	1 (for PS 0-1)	No	Phase 3, randomized	Cisplatin + gemcitabine	ORR	First-line	• Compared with etoposide-cisplatin, gemcitabine-cisplatin provides a significantly higher response rate and a delay in disease progression
Bevacizumab + cisplatin + gemcitabine	None	No	Phase 3 (AVAiL), randomized	Cisplatin + gemcitabine + placebo (CG)	PFS	First-line	• Combining bevacizumab (7.5 or 15 mg/kg) with CG significantly improved PFS and objective response rate. Bevacizumab plus platinum-based chemotherapy offers clinical benefit for bevacizumab-eligible patients with advanced NSCLC.

Bevacizumab + carboplatin + pemetrexed, followed by pemetrexed + bevacizumab (PemCBev)	2A (for adeno-carcinoma only; PS 0-1)	No	Phase 3 (PointBreak), randomized	Bevacizumab + carboplatin + paclitaxel, followed by bevacizumab (PacCBev)	OS	First-line	• OS did not improve with the PemCBev regimen compared with the PacCBev regimen, although PFS was significantly improved with PemCBev
Bevacizumab + cisplatin + pemetrexed followed by bevacizumab maintenance	2A (for adeno-carcinoma only; PS 0-1)	No	Phase 3 (AVAPERL [MO22089]), randomized	Bevacizumab + cisplatin + pemetrexed followed by bevacizumab + pemetrexed maintenance	PFS	First-line	• In patients with nonsquamous NSCLC who had achieved disease control with platinum-based chemotherapy plus bevacizumab, bevacizumab plus pemetrexed maintenance was associated with a significant PFS benefit compared with bevacizumab alone
Continuation Maintenance Therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bevacizumab monotherapy (Bevacizumab + carboplatin + paclitaxel, followed by maintenance therapy with bevacizumab)	1 (if previously given)	No	Phase 2/3 (ECOG 4599), randomized	Carboplatin + paclitaxel, followed by no maintenance therapy	OS	First-line	• The addition of bevacizumab to paclitaxel plus carboplatin in the treatment of selected patients with non-small-cell lung cancer has a significant survival benefit with the risk of increased treatment-related deaths
Bevacizumab + atezolizumab	1 (if previously given)	No	Phase 3 (IMpower150), open-label,	Atezolizumab + carboplatin + paclitaxel,	PFS	First-line	• The addition of atezolizumab to bevacizumab plus chemotherapy significantly improved progression-free

(Atezolizumab + carboplatin + paclitaxel + bevacizumab, followed by maintenance therapy with atezolizumab + bevacizumab [ABCP])			randomized (1:1:1)	followed by atezolizumab (ACP) vs. bevacizumab + carboplatin + paclitaxel, followed by bevacizumab (BCP)			survival and overall survival among patients with metastatic nonsquamous NSCLC, regardless of PD-L1 expression and EGFR or ALK genetic alteration status
Bevacizumab + pemetrexed (Bevacizumab + carboplatin + pemetrexed, followed by pemetrexed + bevacizumab [PemCBev])	2A (if previously given)	No	Phase 3 (PointBreak), randomized	Bevacizumab + carboplatin + paclitaxel, followed by bevacizumab (PacCBev)	OS	First-line	• OS did not improve with the PemCBev regimen compared with the PacCBev regimen, although PFS was significantly improved with PemCBev
Bevacizumab + cisplatin + pemetrexed followed by bevacizumab maintenance	2A (if previously given)	No	Phase 3 (AVAPERL [MO22089]), randomized	Bevacizumab + cisplatin + pemetrexed followed by bevacizumab + pemetrexed maintenance	PFS	First-line	• In patients with nonsquamous NSCLC who had achieved disease control with platinum-based chemotherapy plus bevacizumab, bevacizumab plus pemetrexed maintenance was associated with a significant PFS benefit compared with bevacizumab alone
Bevacizumab + erlotinib *Study is ongoing*	2A (first-line therapy) 2A (continuation therapy	No	Phase 3 (NEJ026), randomized, open-label	Erlotinib	PFS	First-line	• The results of this interim analysis showed that bevacizumab plus erlotinib combination therapy improves progression-free survival compared with erlotinib alone in patients with EGFR-positive NSCLC.

	following progression on erlotinib with bevacizumab)						
Subsequent Therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bevacizumab + standard-of-care (Bev + SOC)	2A	No	Phase 3b (AvaALL), randomized, open-label	Standard-of-care (SOC: (erlotinib or docetaxel or pemetrexed)	OS	Second-line after prior bevacizumab plus platinum-doublet chemotherapy and at least 2 cycles of bevacizumab maintenance	• Results showed that although median OS was longer for patients in the bevacizumab arm plus SOC, it was not significantly longer compared with patients in the SOC alone arm.
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 (2mg/kg or 10mg/kg)	1 preferred (for PS 0-2; PD-L1 ≥ 1%)	Yes (after platinum therapy)	Phase 2/3 (KEYNOTE-010), randomized (1:1:1), open-label	Docetaxel	OS PFS	Previously treated	• Pembrolizumab prolongs overall survival compared to docetaxel and has a favorable benefit-to-risk profile 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
Ramucirumab + docetaxel	2A (first progression only)	Yes (after platinum therapy)	Phase 3 (REVEL), multicenter, double-blind, randomized (1:1)	Docetaxel + placebo	OS	Second-line after platinum-based regimen	• Ramucirumab plus docetaxel improves survival as second-line treatment of patients with stage IV NSCLC

Cervical Cancer

Recurrent or Metastatic Disease, First-line Therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bevacizumab + cisplatin + paclitaxel	1 preferred	Yes	Phase 3 (GOG-0240), randomized, controlled, open-label	Cisplatin + paclitaxel vs. topotecan + paclitaxel +/- bevacizumab vs. topotecan + paclitaxel	OS	Recurrent or persistent disease	• Bevacizumab improved survival in patients with advanced cervical cancer with by 3.5 months compared to chemotherapy alone.
Cisplatin + paclitaxel (TP)	1 other		Phase 3 (GOG 169), randomized	Cisplatin	ORR PFS OS	First-line	• Combination therapy with cisplatin and paclitaxel is superior to cisplatin alone with respect to response rate and PFS.

Cisplatin + paclitaxel (TP)	1 other	No	Phase 3 (JCOG0505), randomized	Carboplatin + paclitaxel (TC)	OS	≤ 1 platinum-regimen and no prior taxane	TC was non-inferior to TP in patients with metastatic or recurrent cervical cancer. However, among patients who had not received prior cisplatin therapy, TC demonstrated to be inferior to TP.
Bevacizumab + topotecan + paclitaxel	1 other	Yes	See data for bevacizumab + cisplatin + paclitaxel; Phase 3 (GOG-0240)				
Carboplatin + paclitaxel	1 other (for patients who have received prior cisplatin therapy)	No	See data for cisplatin + paclitaxel; Phase 3 (JCOG0505)				
Bevacizumab + carboplatin + paclitaxel	2A preferred	No	See data for bevacizumab + cisplatin + paclitaxel; Phase 3 (GOG-0240) See data for cisplatin + paclitaxel; Phase 3 (JCOG0505)				
Topotecan + paclitaxel	2A other	No	See data for bevacizumab + cisplatin + paclitaxel; Phase 3 (GOG-0240)				
Second-line Therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bevacizumab	2B	No	Phase 2	N/A	6-mon PFS	Second- or third-line	• Bevacizumab is active in second- and third-line treatment with an ORR of 11%
Pembrolizumab	2A preferred (for MSI-H /dMMR or PD-	Yes (for PD-L1	Phase 2 (KEYNOTE-158), multi-	N/A	ORR	Second-line or later	• Pembrolizumab demonstrated anti-tumor activity with an ORR of 16%

	L1 positive tumors)	positive tumors)	center, open-label, multi-cohort				PD-L1 expressing refractory cervical cancer

Breast Cancer

HER-2 Negative Recurrent or Metastatic Disease for patients with high tumor burden, rapidly progressive disease, or visceral crisis							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bevacizumab + paclitaxel (AT)	2A	No	Phase 3 (E2100), open-label, randomized	Paclitaxel (T)	PFS	First-line	• Initial therapy of metastatic breast cancer with paclitaxel plus bevacizumab prolongs progression-free survival by 5.9 months, but not overall survival, as compared with paclitaxel alone
Bevacizumab + chemotherapy (capecitabine, taxane, or anthracycline)	2A	No	Phase 3 (RIBBON-1), randomized, double-blind, placebo-controlled	Chemotherapy + placebo	PFS	First-line	• The combination of BV with capecitabine, a taxane, or anthracycline improves clinical benefit in terms of increased PFS in first-line treatment of metastatic breast cancer however a significant increase in OS was not observed.
Bevacizumab + docetaxel	None	No	Phase 3 (AVADO), randomized, double-blind	Docetaxel + placebo	PFS	First-line	• Bevacizumab 15 mg/kg every 3 weeks increased PFS when combined with docetaxel as first-line therapy for MBC compared with docetaxel plus placebo.
Doxorubicin + cyclophosphamide (AC)	2A	No	Phase 3, randomized, multi-center	Doxorubicin + docetaxel (AT)	TTP	First-line	• AT significantly improves TTP and ORR compared with AC in patients with MBC, but there is no difference in OS

Epirubicin + cyclophosphamide (EC)	2A	No	Phase 3 (AB01), randomized, multi-center	Epirubicin + paclitaxel (EP)	PFS	First-line	• In terms of progression-free survival and overall survival, there was no evidence of a difference between EP and EC. The data demonstrate no additional advantage to using EP instead of EC as first-line chemotherapy for MBC in taxane-naïve patients.
Docetaxel + capecitabine (DC)	2A	No	Phase 3, randomized, multi-center	Docetaxel + epirubicin (DE)	TTP	First-line	• The DE and DC regimens have similar efficacy but different toxicity. Either regimen can be used as front-line treatment of ABC.
Gemcitabine + paclitaxel (GT)	2A	No	Phase 3, randomized	Paclitaxel (T)	OS	First-line (after adjuvant anthracycline)	• Gemcitabine added to paclitaxel is effective therapy for women with advanced breast cancer who previously received anthracyclines with a significant improvement in OS and TTP.
Nab-paclitaxel + bevacizumab	2A	Yes	Phase 3, randomized	Ixabepilone + bevacizumab vs. paclitaxel + bevacizumab	PFS	First-line	• PFS and OS for nab-paclitaxel was not superior to paclitaxel with a trend toward inferiority • Toxicity was increased for nab-paclitaxel

Renal Cell Carcinoma

First-line therapy relapsed or stage IV disease – clear cell histology							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bevacizumab + interferon alfa	None	Yes	Phase 3 (AVOREN), multi-center, randomized, double-blind	Interferon-alfa (IFN-α) + placebo	OS	First-line for metastatic disease	• The combination of bevacizumab with interferon alfa as first-line treatment in patients with metastatic renal cell carcinoma results in a significant improvement in progression-free

							survival, compared with interferon alfa alone.
Bevacizumab + interferon alfa	None	Yes	Phase 3 (CALGB 90206), randomized	IFN-α	OS	First-line for metastatic disease	• Avastin in combination with interferon alfa produced a superior PFS and higher ORR than interferon alfa alone. However, there were no significant differences in OS between the two groups and more toxicity associated with the combination arm.
Pembrolizumab + axitinib	1 preferred	Yes	Phase 3 (KEYNOTE-426), randomized, multi-center, open-label	Sunitinib	PFS OS	First-line therapy for advanced RCC	• 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 2A other 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 2A other for poor/	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.

	intermediate risk						
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.
Nivolumab + ipilimumab	1 preferred for intermediate/ poor-risk 2A for favorable risk	Yes for intermediate/ poor-risk	Phase 1 (CheckMate 016)	N/A	Safety	All lines of therapy	• Nivolumab plus ipilimumab demonstrated an ORR of 40.4% in patients of all risk-groups, including patients who received prior therapy.
Avelumab + axitinib	2A other	Yes	Phase 3 (JAVELIN Renal 101), randomized, multi-center, open-label	Sunitinib	PFS OS	First-line therapy of advanced RCC	• Progression-free survival was significantly longer with avelumab plus axitinib than with sunitinib among patients who received these agents as first-line treatment for advanced renal-cell carcinoma.
Temsirolimus	2A certain circumstances for poor risk	Yes	Phase 3 (Global ARCC), multi-center	IFN-α vs. temsirolimus + IFN-α	OS	First-line	• As compared with interferon alfa, temsirolimus improved overall survival among patients with metastatic renal-cell carcinoma and a poor prognosis
Cabozantinib	2A preferred for poor/ intermediate 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.

	2B for favorable risk						
Relapsed or stage IV non-clear cell histology							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bevacizumab	2A certain circumstances	No	Phase 2	N/A	12-mon PFS	First- or second-line	• PFS with bevacizumab alone ranged from 6-25 months and suggest activity with minimal toxicity.
Bevacizumab + everolimus	2A certain circumstances	No	Phase 2, single-center	N/A	PFS	First-line	• Tumors with significant papillary or chromophobe elements showed higher PFS and ORR than other histologies. • Subjects with other variants (medullary RCC and unclassified RCC without papillary features), achieved little or no benefit from everolimus plus bevacizumab.
Sunitinib	2A preferred	Yes	Phase 2	N/A	ORR	No prior sunitinib, sorafenib, or bevacizumab	• Clinical activity with sunitinib in non-clear cell RCC is supported by an ORR of 36% and PFS of 6.4 months.
Sunitinib	2A preferred	Yes	Phase 2 (ASPEN), multi-center, open-label, randomized	Everolimus	PFS	First-line	• Sunitinib improved PFS compared with everolimus in patients with metastatic non-clear cell RCC.
Bevacizumab + erlotinib	2A certain circumstances	No	Phase 2	N/A	ORR	First- and second-line	• Combination of bevacizumab plus erlotinib demonstrated activity in patients with advanced papillary RCC, particularly in patients with HLRCC

							(ORR 60% for HLRCC and 29% for sporadic papillary RCC).
Everolimus	2A other	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.
Temsirolimus	1 (for poor prognosis features) 2A (all others)	No	Retrospective analysis of phase 3 Global ARCC Trial	N/A	----------	First-line	• Temsirolimus appears to be efficacious in patients with clear cell and non-clear cell histologies and can, therefore, be used for the treatment of all types of RCC

CNS Cancer

Recurrent anaplastic glioma							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bevacizumab + chemotherapy	2B	No	Retrospective analysis	N/A	----------	Recurrent gliomas	• Combination therapy with bevacizumab and chemotherapy demonstrated a 6 month PFS rate of 32% for patients with anaplastic glioma and 42% for patients with glioblastoma.
Bevacizumab	2A	No	Retrospective analysis	N/A	PFS	Recurrent alkylator-refractory anaplastic oligodendroglioma	• Bevacizumab demonstrated efficacy in patients with recurrent alkylator-refractory anaplastic oligodendroglioma
Bevacizumab	2A	No	Retrospective analysis	N/A	----------	Recurrent alkylator-refractory anaplastic astrocytoma	• Bevacizumab demonstrated efficacy with a 6 month PFS rate of 60%.

Bevacizumab + irinotecan	2A	No	Retrospective analysis	N/A	----------	Recurrent oligodendroglioma	• Bevacizumab plus irinotecan is clinically active with a 6-mon PFS rate of 42%
Bevacizumab + irinotecan	2A	No	Phase 2	N/A	----------	Recurrent grade III-IV glioma	• The combination of bevacizumab and irinotecan is an active regimen for recurrent grade III-IV glioma with a 6-mon PFS of 38% and 6-mon OS of 72%.
Bevacizumab + fotemustine (not FDA approved, available in Europe)	2A	No	Phase 2	N/A	ORR 6-mon PFS	Recurrent glioma	• Combination of bevacizumab and fotemustine in recurrent gliomas resulted an ORR of 35%
Temozolomide	2A	Yes (anaplastic astrocytoma after progression on nitrosourea and procarbazine)	Phase 2, open-label, multi-center	N/A	6-mon PFS	First relapse of anaplastic astrocytoma or anaplastic mixed oligoastrocytoma	• Temozolomide demonstrated good single-agent activity with a 12-month PFS and OS rate of 24% and 56%, respectively, at first relapse in patients with malignant astrocytoma
Carmustine + α-difluoromethyl-ornithine (DFMO)	2A	No	Clinical trial	N/A	----------	Recurrent anaplastic gliomas and glioblastomas	• Carmustine + DFMO demonstration clinical activity with a partial response rate of 9.5% and stable disease in 47.6% in patients with anaplastic gliomas.
Procarbazine + lomustine +	2A	No	Phase 2	N/A	----------	Recurrent low-grade oligodendrogliomas	• Chemotherapy with PCV is effective in the treatment of recurrent low-grade oligodendrogliomas and oligoastrocytomas

vincristine (PCV)						and oligoastrocytomas	
Recurrent glioblastoma							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bevacizumab	2A	Yes	Phase 2 (AVF3708g, BRAIN study), multi-center, open-label, non-comparative	Bevacizumab (bev) + irinotecan (CPT)	6-mon PFS ORR	Recurrent GBM	• Bevacizumab alone or in combination with irinotecan appeared to be better than historical control serious with a 6-mon PFS rate of 43-50%.
Bevacizumab + lomustine (bev + CCNU)	2A	No	Phase 3 (EORTC 26101), multi-center, randomized, open-label	Lomustine	OS	Recurrent GBM	• Treatment with bevacizumab plus lomustine prolonged PFS however did not confer a survival advantage over treatment with lomustine alone in patients with progressive GBM.
Bevacizumab + lomustine (bev + CCNU)	2A	Yes	Phase 2 (BELOB), randomized, open-label, multi-center	Single-agent bevacizumab or lomustine	9-mon OS	Recurrent GBM	• Bevacizumab plus lomustine demonstrated increased effectiveness with a 9 month OS rate of 63% compared to either agent alone. (However, a benefit in OS was not observed in the phase III EORTC 26101 trial).
Bevacizumab	2A	Yes	Phase 2	N/A	6-mon PFS	Recurrent GBM	• Single-agent bevacizumab has clinical activity in patients with recurrent GBM with a PFS of 16 weeks and OS of 31 weeks

Bevacizumab + irinotecan	2A	No	Phase 2	N/A	----------	Recurrent GBM	• Bevacizumab and irinotecan are an effective treatment for recurrent glioblastoma with a 6-mon PFS of 46% and 6-mon OS of 77%.
Bevacizumab + fotemustine	2A	No	Phase 2	N/A	ORR 6-mon PFS	Recurrent glioma	• Combination of bevacizumab and fotemustine in recurrent gliomas resulted an ORR of 35%
Bevacizumab + temozolomide	2A	No	Phase 2	N/A	-----	Recurrent glioblastoma after radiation therapy and temozolomide	• Temozolomide and bevacizumab demonstrated a 6-month PFS rate of 18.8% in patients with recurrent glioblastoma.
Bevacizumab + temozolomide	2A	No	Phase 2	N/A	-----	Recurrent glioblastoma	• Bevacizumab plus temozolomide resulted a 6-month PFS rate of 52% in patients with recurrent glioblastoma.
Temozolomide (TMZ)	2A	No	Phase 2, randomized, multi-center, open-label	Procarbazine	6-mon PFS	First-relapse	• Temozolomide is effective in the treatment of patients with recurrent glioblastoma with a 6-month PFS rate of 21%.
Temozolomide (TMZ)	2A	No	Phase 2 (DIRECTOR trial)	N/A	TTF	Rechallenge with TMZ at first-progression	• Temozolomide rechallenge is a treatment option for MGMT promoter-methylated recurrent glioblastoma with a TTF of 3.2 months.
Temozolomide (TMZ)	2A	No	Phase 2 (RESCUE), multi-center	N/A	----------	Recurrent glioma (after previous TMZ treatment)	• Rechallenge with TMZ demonstrated a 6-month PFS rate between 23-36%.
Temozolomide (TMZ)	2A	No	Retrospective study	N/A	--------	Non-progressive disease at first MRI after completion of TMZ concurrent with and adjuvant to	• TFI ≥5 months represents a predictor of retained TMZ sensitivity

						radiotherapy, a treatment-free interval (TFI) of at least 8 weeks and received TMZ rechallenge at the time of progression	
Lomustine (CCNU)	2A	Yes	See Phase 3 (EORTC 26101) above				
Carmustine (BCNU)	2A	Yes	Phase 2	N/A	---------	Recurrent glioblastoma	• Carmustine demonstrated a 6-month PFS rate of 17.5%
Procarbazine + lomustine + vincristine (PCV)	2A	No	Retrospective cohort study	Bevacizumab + irinotecan	----------	Second-line	• Bevacizumab plus irinotecan had higher response rates, almost twice the OS, and a lower degree of toxicity in contrast to the PCV group.
Procarbazine + lomustine + vincristine (PCV)	2A	No	Retrospective analysis	N/A	----------	Recurrent glioblastoma	• PCV indicated to be useful in patients with recurrent glioblastoma with a 6-month PFs rate of 38.4%.
Regorafenib	2A preferred	No	Phase 2 (REGOMA), multi-center, open-label, randomized, controlled	Lomustine	OS	Recurrent glioblastoma	• Regorafenib demonstrated a higher OS compared to lomustine in patients with recurrent glioblastoma.
Adult intracranial and spinal Ependymoma (excluding subependymoma)							

Regimen	NCCN Category	FDA Approved	Trial Design	Comparator	Primary End-Point	Line of Therapy	Conclusion
Bevacizumab (alone or with cytotoxic chemotherapy)	2A	No	Retrospective analysis	N/A	----------	Recurrent ependymoma	• Use of bevacizumab-containing regimens appears to delay tumor progression (TTP 6.4mon) and demonstrated a partial response rate of 75%
Cisplatin	2A	No	Retrospective analysis	Without cisplatin	----------	Recurrent ependymoma	• Cisplatin-based chemotherapy achieved a higher response rate, but did not prolong disease progression-free survival or OS compared to regimens without cisplatin
Meningioma – recurrent or progressive							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bevacizumab ± chemotherapy	2A (as a single agent)	No	Retrospective review	N/A	-----	Recurrent or progressive disease	• Bevacizumab appears to be associated with anti-tumor effect with a 6-month PFS rate of 86% when administered as a single agent or in combination with chemotherapy.
Bevacizumab	2A	No	Retrospective review	N/A	-----	---------	• Patients treated with bevacizumab demonstrated a 6-month PFS rate of 43.8% with the best response being stable disease
Radiation necrosis							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**

Bevacizumab	2A	No	Retrospective analysis	N/A	----------	For acute neurologic deterioration in patients with GBM	• Single agent bevacizumab improved function and quality of life in patients with glioblastoma
Bevacizumab (Q 3 weeks for 4 doses)	2A	No	Phase 2, randomized, double-blind, placebo-controlled	Saline	Change in edema volume on MRI at 6 weeks	Radiation necrosis	• Bevacizumab demonstrated efficacy with a response in all 5 patients who received bevacizumab in the treatment of radiation necrosis
Bevacizumab (5mg/kg Q 2 weeks for 4 cycles)	2A	No	Phase 2, randomized, controlled, open-label, multi-center trial	Corticosteroid	2-month ORR	Radiation necrosis after nasopharyngeal cancer therapy	• Compared with corticosteroids, bevacizumab offers improved symptomatic relief and radiographic response.

Ovarian Cancer

Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer – Single agent therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bevacizumab	2A preferred	No	Phase 2 (GOG 170-D)	N/A	PFS ORR	Second- or third-line	• Bevacizumab demonstrated to be clinically active (ORR 21%) in second- and third-line treatment of patients with epithelial ovarian cancer and primary peritoneal cancer.
Topotecan	2A	Yes	Phase 3, randomized, multicenter	Liposomal doxorubicin	--------	Second-line or later	• Liposomal doxorubicin prolonged survival compared with topotecan in patients with recurrent and

							refractory epithelial ovarian cancer by almost 7 weeks • Survival benefit is pronounced in patients with platinum-sensitive disease
Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer – Platinum Sensitive							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Carboplatin + gemcitabine + bevacizumab, followed by bevacizumab until progression	2A preferred	Yes	Phase 3 (OCEANS), randomized, multicenter, blinded, placebo-controlled Final analysis	Carboplatin + gemcitabine + placebo	PFS	Second-line; recurrence after at least 6 months of first-line platinum-based therapy	• Carboplatin, gemcitabine, plus bevacizumab followed by bevacizumab until progression resulted in a statistically significant improvement in PFS compared with carboplatin, gemcitabine, plus placebo • The final survival analysis did not show an increase in OS with the chemotherapy plus bevacizumab arm when compared with chemotherapy alone.
Carboplatin + paclitaxel + bevacizumab, followed by bevacizumab until progression	2A preferred	Yes	Phase 3 (GOG-0213), multicenter, open-label, randomized	Carboplatin + paclitaxel	OS	Second-line or later; relapsing after 6 months of being treatment-free	• The addition of bevacizumab to standard chemotherapy, followed by maintenance therapy until progression, improved the median OS in patients with platinum-sensitive recurrent ovarian cancer, although not statistically significant
Carboplatin + liposomal doxorubicin	2A preferred	Yes (progressed or recurred after platinum-	Phase 3 (CALYPSO), randomized, multicenter	Carboplatin + paclitaxel	PFS	Second- or third-line therapy with recurrence after more than 6 months since first- or second-line	• Carboplatin + liposomal doxorubicin demonstrated superiority in PFS compared to carboplatin + paclitaxel.

		based chemotherapy)				platinum-based therapy	
Carboplatin + liposomal doxorubicin + bevacizumab (CD-BEV)	2A preferred	No	Phase 3 (AGO-OVAR 2.21), randomized	Carboplatin + gemcitabine + bevacizumab (CG-BEV)	PFS	Recurrent disease after at least 6 months after first-line platinum-based chemotherapy (50% had prior anti-angiogenic treatment)	• CD-BEV provided a significant PFS improvement compared to CG-BEV in patients with recurrent ovarian cancer suitable for platinum-based retreatment. CD-BEV was also associated with fewer serious adverse events.
Bevacizumab + niraparib	2A	No	Phase 2, randomized, open-label	Niraparib	PFS	Recurrent disease after at least 6 months after last platinum-based chemotherapy	• Niraparib plus bevacizumab significantly improved progression-free survival compared with niraparib alone.
Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer – Platinum Resistant							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bevacizumab + chemotherapy (paclitaxel, liposomal doxorubicin, or topotecan)	2A preferred	Yes	Phase 3 (AURELIA), randomized, multi-center, open-label	Chemotherapy alone (paclitaxel, liposomal doxorubicin, or topotecan)	PFS	Platinum-resistant, recurrent disease (no more than 2 prior chemo regimens)	• Adding bevacizumab to chemotherapy statistically significantly improved PFS and ORR; the OS trend was not significant.

Bevacizumab + oral cyclophosphamide	2A preferred	No	Retrospective review	N/A	-----	Platinum-resistant disease	• Bevacizumab and cyclophosphamide demonstrated to be effective in heavily pretreated patients with recurrent ovarian carcinoma
Bevacizumab + oral cyclophosphamide	2A preferred	No	Phase 2	N/A	6-mon PFS	Platinum-resistant, recurrent disease (no more than 2 prior chemo regimens)	• The combination of bevacizumab and oral cyclophosphamide is active in recurrent ovarian cancer with a 6-month PFS rate or 56%.
Docetaxel	2A	No	Phase 2	N/A	---------	Second-line	• Docetaxel is active in paclitaxel-resistant ovarian and peritoneal cancer but, in view of significant hematologic toxicity
Etoposide (oral)	2A	No	Phase 2	N/A	---------	Second-line therapy	• Etoposide is active in platinum-sensitive ovarian cancer with an ORR of 26.8%
Topotecan	2A	Yes	Phase 3, randomized, multicenter	Liposomal doxorubicin	--------	Second-line or later	• Liposomal doxorubicin prolonged survival compared with topotecan in patients with recurrent and refractory epithelial ovarian cancer by almost 7 weeks • Survival benefit is pronounced in patients with platinum-sensitive disease
Topotecan weekly (Tw)	2A	Yes	Phase 2 (TOWER), randomized	Topotecan conventional 5-day therapy (Tc)	ORR	Second-line and later	• Conventional dosing of topotecan was more effective than weekly dosing in terms of response. There was no difference in median PFS or median OS.
Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer –Adjuvant and Maintenance Therapy							

Regimen	NCCN Category	FDA Approved	Trial Design	Comparator	Primary End-Point	Line of Therapy	Conclusion
Bevacizumab + paclitaxel + carboplatin (bevacizumab given upfront and as maintenance)	2A	Yes	Phase 3 (GOG-0218), double-blind, placebo-controlled, randomized Subgroup analysis	Carboplatin + paclitaxel intravenous	PFS	Newly diagnosed stage III or IV epithelial ovarian cancer following initial surgical resection	• In the GOG-0218 study, median PFS with bevacizumab plus chemotherapy followed by single-agent bevacizumab was 14.1 months versus 10.3 months with chemotherapy alone. • A subgroup analysis suggested that upfront therapy with bevacizumab, carboplatin, and paclitaxel may be beneficial in patients with ascites.
Bevacizumab + paclitaxel + carboplatin intravenous (bevacizumab given upfront and as maintenance)	2A	Yes	Phase 3 (ICON7), randomized Overall survival results	Carboplatin + paclitaxel intravenous	PFS	After surgery; patients with high-risk early-stage disease (clear cell or grade 3 tumors) or advanced disease	• Bevacizumab improved progression-free survival in women with ovarian cancer, however, did not increase overall survival in the study population as a whole. An overall survival benefit was recorded in poor-prognosis patients.
Cisplatin + paclitaxel (IV/IP)	2A	Yes	Phase 3 (GOG 172), randomized	Cisplatin + paclitaxel (IV)	PFS OS	First-line, optimally resected (< 1cm residual mass)	• As compared with intravenous paclitaxel plus cisplatin, intravenous paclitaxel plus intraperitoneal cisplatin and paclitaxel improves survival in patients with optimally debulked stage III ovarian cancer
Paclitaxel + carboplatin	2A	Yes	Phase 3, randomized, non-inferiority trial	Paclitaxel + cisplatin	---------	First-line, optimally resected (< 1cm residual mass)	• In patients with advanced ovarian cancer, a chemotherapy regimen consisting of carboplatin plus paclitaxel results in less toxicity, is easier to administer, and is not inferior, when compared with cisplatin plus paclitaxel

Paclitaxel + carboplatin	2A	Yes	Phase 3 (MITO-2), randomized	Pegylated liposomal doxorubicin (PLD) + carboplatin	PFS	First-line	• Carboplatin/PLD was not superior to carboplatin/paclitaxel, which remains the standard first-line chemotherapy for advanced ovarian cancer.
Docetaxel + carboplatin	2A	Yes	Phase 3, randomized	Paclitaxel + carboplatin	PFS	First-line	• Docetaxel-carboplatin appears to be similar to paclitaxel-carboplatin in terms of progression-free survival and response
Bevacizumab + olaparib *Maintenance after prior bevacizumab as primary therapy*	1 for BRCA mutation 2A for BRCA wild-type or unknown	Yes	Phase 3 (PAOLA-1), randomized, double-blind	Placebo	PFS OS	Newly diagnosed advanced, high-grade serous or endometrioid ovarian cancer, primary peritoneal cancer, or fallopian-tube cancer with no evidence of disease or to have had a clinical complete or partial response after first-line platinum-taxane chemotherapy plus bevacizumab	• In patients with advanced ovarian cancer receiving first-line standard therapy including bevacizumab, the addition of maintenance olaparib provided a significant progression-free survival benefit, which was substantial in patients with HRD-positive tumors, including those without a BRCA mutation.
Pegylated liposomal doxorubicin (PLD) + carboplatin	2A	No	See paclitaxel + carboplatin above				

Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer – Neoadjuvant therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bevacizumab + carboplatin + paclitaxel	1 for neoadjuvant therapy 2A for stable disease following neoadjuvant therapy	No	Phase 2 (GEICO 1205/NOVA TRIAL), randomized, open-label	Carboplatin + paclitaxel	ORR	Neoadjuvant followed by maintenance therapy	• Neoadjuvant therapy with bevacizumab improved surgical feasibility in patients initially considered unresectable.
Cisplatin or carboplatin	None	No	Phase 3 (EORTC-NCIC), randomized	Primary debulking surgery	OS	Neoadjuvant therapy of stage IIIC or IV disease	• Neoadjuvant chemotherapy followed by interval debulking surgery was not inferior to primary debulking surgery followed by chemotherapy as a treatment option for patients with bulky stage IIIC or IV ovarian carcinoma
Carboplatin + paclitaxel	2A	No	Phase 3 (JCOG0602), randomized	Primary debulking surgery	OS	Neoadjuvant therapy	• Superiority of neoadjuvant chemotherapy or primary debulking surgery could not be confirmed.
Relapsed sex cord-stromal tumors							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bevacizumab	2A	No	Retrospective review	N/A	--------	Recurrent disease after cytotoxic chemotherapy	• Bevacizumab demonstrated activity for the treatment of recurrent

							ovarian granulosa cell tumors with an ORR of 38%.
Bevacizumab	2A	No	Phase 2 (GOG 251)	N/A	ORR	Recurrent disease; No prior bevacizumab	• Bevacizumab has activity in the treatment of recurrent sex cord-stromal tumors of the ovary with an ORR of 16.7%.
Leuprolide acetate	2A (granulosa cell tumors only)	No	Small study	N/A	-------	First- or second-line	• Leuprolide acetate appears to have activity in patients with refractory ovarian granulosa cell tumor with an ORR of 40%.

Soft Tissue Sarcoma

Angiosarcoma							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bevacizumab	2A	No	Phase 2, open-label, multi-center	N/A	PFS	First- through fourth-line therapy	• Bevacizumab is an effective and well-tolerated treatment for metastatic or locally advanced angiosarcoma and epithelioid hemangio-endothelioma. 17% had a partial response and 50% showed stable disease.
Paclitaxel	2A	No	Phase 2 (ANGIOTAX)	N/A	PFS	All lines of therapy	• Paclitaxel demonstrated efficacy in patients with metastatic or unresectable angiosarcoma with a 2-month PFS rate of 74%.
Docetaxel	2A	No	Phase 2, multi-center	N/A	---------	Second-line	• Docetaxel has activity in adult soft tissue sarcoma in second-line therapy with a 17% partial response rate.

Sorafenib	2A	No	Phase 2	N/A	ORR	First- through fourth-line therapy	• As a single agent, sorafenib has activity against angiosarcoma and minimal activity against other sarcomas.
Sunitinib	2A	No (FDA approved for GIST)	Phase 2, open-label, multi-center	N/A	ORR	First- through third-line therapy	• Sunitinib demonstrated evidence of response in patients with non-GIST sarcoma. Specific results for patients with angiosarcoma however was not noted.
Pazopanib	2A	Yes for subsequent therapy	Phase 3 (PALETTE), randomized, double-blind	Placebo	PFS	Second-line or later therapy after prior anthracycline chemotherapy; Angiogenesis inhibitor-naive	• Pazopanib significantly prolonged median PFS compared to placebo in patients with metastatic STS who had failed at least one anthracycline-based chemotherapy. However, trend toward improved OS was not statistically significant.
Solitary Fibrous Tumor/Hemangiopericytoma							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bevacizumab + temozolomide	2A	No	Retrospective analysis	N/A	---	All lines of therapy	• Combination therapy with temozolomide and bevacizumab is a clinically beneficial regimen with a 79% partial response rate.
Sunitinib	2A	No	Retrospective analysis	N/A	---	All lines of therapy	• Sunitinib demonstrated clinical activity in patients with solitary fibrous tumors with 3 patients achieving a partial response and 16 patients with stable disease.
Sorafenib	2A	No	Subgroup analysis from a Phase 2	N/A	---	Second-line and later	• Data suggested a potential efficacy of sorafenib with 2 out of 5 patients achieving 9 months of disease control.

Pazopanib	2A	No	Retrospective analysis	N/A	---	First- and second-line	• Pazopanib is an effective treatment option for recurrent or metastatic solitary fibrous tumor in first- and second-line settings with an ORR of 50%.

Endometrial Carcinoma

Recurrent, Metastatic, or High-Risk Disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bevacizumab + carboplatin + paclitaxel	2A (for advanced or recurrent disease only)	No	Phase 2 (MITO Group END-2 trial), randomized	Carboplatin + paclitaxel	---	First- and second-line	• The addition of bevacizumab to carboplatin plus paclitaxel significantly increased PFS in advanced or recurrent endometrial cancer.
Bevacizumab + carboplatin + paclitaxel	2A (for advanced or recurrent disease only)	No	Retrospective analysis	N/A	---	First- and second-line	• Combination therapy with bevacizumab, paclitaxel, and carboplatin demonstrated an ORR of 82.8%, PFS of 20 months, and OS of 56 months.
Carboplatin + paclitaxel (TC)	2A preferred	No	Phase 3 (GOG 209), non-inferiority, randomized	Cisplatin + doxorubicin + paclitaxel + filgrastim (TAP)	---	First-line	• TC is not inferior to TAP in terms of PFS and OS. Overall, the toxicity profile favors TC.

Cisplatin + doxorubicin + paclitaxel (TAP)	2A	No	Phase 3 (GOG 177)	Cisplatin + doxorubicin (AP)	OS	Chemo-therapy naive	• TAP significantly improves ORR, PFS, and OS compared with AP
Bevacizumab	2A (after progression on prior cytotoxic chemo)	No	Phase 2	N/A	6-mon PFS 6-mon OS	Second- or third-line therapy	• Bevacizumab is clinically active based on PFS at 6 months of 40.4% in recurrent or persistent endometrial carcinoma
Paclitaxel	2A	No	GOG study	N/A	----------	Second-line	• Paclitaxel is an active agent in the treatment of endometrial cancer in patients who have had prior chemotherapy with an ORR of 27.3%
Liposomal doxorubicin	2A	No	Phase 2	N/A	----------	Second-line	• Liposomal doxorubicin has only limited activity (ORR 9.5%) in pretreated advanced, recurrent endometrial cancer
Temsirolimus	2A	No	Phase 2	N/A	ORR	All lines of therapy	• Temsirolimus demonstrated clinical activity with ORR higher in chemo-naïve patients than in chemo-treated patients

Malignant Pleural Mesothelioma

First-Line Therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bevacizumab + cisplatin + pemetrexed, followed by	1 (for unresectable disease only)	No	Phase 3 (MAPS), multi-center, randomized,	Cisplatin + pemetrexed	OS	Chemo-naïve	• Addition of bevacizumab to pemetrexed plus cisplatin significantly improved OS in malignant pleural mesothelioma at the cost of expected manageable toxic effects, therefore it

maintenance bevacizumab			controlled, open-label				should be considered as a suitable treatment for the disease.
Cisplatin + pemetrexed	1	Yes	Phase 3, randomized	Cisplatin	---------	Chemo-naïve	Treatment with pemetrexed plus cisplatin and vitamin supplementation resulted in superior survival time, time to progression, and response rates compared with treatment with cisplatin alone in patients with malignant pleural mesothelioma.
Bevacizumab + carboplatin + pemetrexed	2A	No	Phase 2	N/A	PFS	First-line	• Bevacizumab, carboplatin, and pemetrexed achieved a 34.2% partial response and 57.9% stable disease. • The primary end point of the trial was not reached
Carboplatin + pemetrexed	2A	No	Phase 2	N/A	--------	First-line	• This combination of carboplatin and pemetrexed is moderately active with an ORR of 25%
Carboplatin + pemetrexed	2A	No	Phase 2, multi-center	N/A	ORR	Chemo-naïve	• Disease control rate, time to disease progression, and overall survival were similar to the results achieved with the standard regimen of pemetrexed and cisplatin, suggesting that the carboplatin combination could be an alternative option for these patients.

Vulvar Cancer

Advanced, Recurrent/Metastatic Disease - Squamous cell carcinoma							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**

Bevacizumab + cisplatin + paclitaxel *Cervical cancer data*	2A preferred	No	Phase 3 (GOG-0240), randomized, controlled, open-label	Cisplatin + paclitaxel vs. topotecan + cisplatin + paclitaxel vs. topotecan + paclitaxel	OS	Persistent, recurrent, or metastatic *cervical cancer* (74% had received prior chemoradiation)	• Bevacizumab improved survival in patients with advanced *cervical cancer* with by 3.5 months compared to chemotherapy alone.
Cisplatin	2A preferred	No	No clinical literature to support use.				
Carboplatin	2A preferred	No	No clinical literature to support use.				
Cisplatin + paclitaxel (TP) *Cervical cancer data*	2A preferred	No	Phase 3 (JCOG0505), randomized	Carboplatin + paclitaxel (TC)	OS	≤ 1 platinum-regimen and no prior taxane	TC was non-inferior to TP in patients with metastatic or recurrent *cervical cancer*
Carboplatin + paclitaxel	2A preferred	No	See cisplatin + paclitaxel above				

Small Bowel Adenocarcinoma (SBA)

Advanced or Metastatic Disease – Initial Therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bevacizumab + FOLFOX	2A (if appropriate for intensive therapy)	No	Retrospective study	N/A	-----	First- and second-line	• Bevacizumab plus chemotherapy demonstrated an OS of 21.9 months.

Bevacizumab + CapeOx	2A (if appropriate for intensive therapy)	No	Phase 2, single-center, open-label	N/A	6-mon PFS	Untreated disease	• The results of the current study indicate that CapeOX with bevacizumab is an active regimen (6-mon PFS rate 68%) for patients with SBA.
FOLFOX	2A	No	Phase 2	N/A	-----	First-line	• The modified FOLFOX as first-line therapy demonstrated an ORR of 48.5% in patients with advanced SBA.
FOLFOX	2A	No	Phase 2, multi-center, single-arm, open-label	N/A	1-year PFs	First-line	• Although the primary endpoint was not met, mFOLFOX6 showed effective with an ORR of 45% and 1-year PFS rate of 23% as a first-line treatment for SBA.
CapeOX	2A	No	Phase 2	N/A	ORR	First-line	• CapeOX produced an ORR of 50%, with 10% achieving complete response.

Hepatocellular Adenocarcinoma

First-line therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Bevacizumab + atezolizumab	1 preferred for Child-Pugh Class A only	Yes	Phase 3 (IMbrave150), multicenter, open-label, randomized	Sorafenib	PFS PS	First-line	• In patients with unresectable hepatocellular carcinoma, atezolizumab combined with bevacizumab resulted in better overall and progression-free survival outcomes than sorafenib.