

# Avastin® (bevacizumab) (Intravenous)

\*ONCOLOGY\*

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## I. Length of Authorization

Coverage will be provided for six months and may be renewed. For CNS cancers (symptom management), coverage will be provided for 12 weeks and may NOT be renewed.

## II. Dosing Limits

### A. Quantity Limit (max daily dose) [Pharmacy Benefit]:

- 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) [Medical Benefit]:

#### Oncology indications (J9035):

- 170 billable units per 21 days
- 120 billable units per 14 days

## III. Initial Approval Criteria

- Patient must have a contraindication or intolerance to bevacizumab-awwb (Mvasi™) prior to consideration of Avastin.

Coverage is provided in the following conditions:

- Patient is 18 years or older; **AND**
- Patient must have no recent history of hemorrhage or hemoptysis (the presence of blood in sputum); **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) †

- Not used as part of adjuvant treatment; **AND**
- Will not be used in combination with another biologic agent (i.e., panitumumab, ramucirumab, etc.); **AND**
- Patient's disease is metastatic, unresectable, or advanced; **AND**
  - Used as first-line therapy; **AND**

- In combination with a fluoropyrimidine-based regimen (e.g., 5-fluorouracil/5-FU or capecitabine) †; **OR**
- In combination with irinotecan or irinotecan-based regimen (FOLFIRI) after previous adjuvant FOLFOX or CapeOX within the past 12 months; **OR**
- Used as subsequent therapy; **AND**
  - In combination with a fluoropyrimidine-based regimen (e.g., 5-fluorouracil/5-FU or capecitabine) †; **OR**
  - In combination with irinotecan or FOLFIRI (if previously treated with oxaliplatin-based therapy without irinotecan); **OR**
  - In combination with FOLFOX or CapeOX (if previously treated with irinotecan-based therapy without oxaliplatin); **OR**
  - In combination with FOLFOX, CapeOX, irinotecan, FOLFIRI, or irinotecan and oxaliplatin (if previously treated with fluoropyrimidine-based therapy without irinotecan or oxaliplatin); **OR**
- Used for metastatic disease that has progressed on first-line bevacizumab containing regimen in combination with an irinotecan and/or oxaliplatin-based regimen (if not used first-line)

#### **Non-Squamous Non-Small Cell Lung Cancer (NSCLC) †**

- 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); **AND**
  - Used as first-line therapy for EGFR, ALK negative or unknown, PD-L1 expression  $\geq 1\%$  and PS  $\leq 2$  in combination with atezolizumab, carboplatin, and paclitaxel; **OR**
  - Used as first-line therapy in patients with PS  $\leq 1$  for genomic tumor aberration (e.g., EGFR, ALK, ROS1, BRAF) negative or unknown and PD-L1  $<1\%$  or unknown **OR** BRAF V600E-mutation positive in combination with:
    - Atezolizumab, carboplatin and paclitaxel; **OR**
  - Used as subsequent therapy in patients with PS  $\leq 1$  for genomic tumor aberration (e.g., EGFR, ALK, ROS1) positive and prior targeted therapy **OR** BRAF V600E-mutation positive **OR** PD-L1  $\geq 1\%$  and EGFR, ALK negative or unknown with no prior platinum-doublet chemotherapy in combination with:
    - Carboplatin and paclitaxel; **OR**
    - Atezolizumab, carboplatin and paclitaxel; **OR**
  - Used as continuation maintenance therapy (*bevacizumab must have been included in patient's first-line chemotherapy regimen*) for PS  $\leq 2$  and patient's disease has not progressed (achieved tumor response or stable disease) after first-line systemic therapy; **AND**
    - Used as a single agent; **OR**
    - Used in combination with atezolizumab if bevacizumab was previously used first-line as part of atezolizumab/carboplatin/paclitaxel/bevacizumab regimen

#### **Cervical Cancer †**

- Patient's disease must be persistent, recurrent, or metastatic; **AND**
- Used in combination with paclitaxel **AND** either cisplatin, carboplatin, or topotecan

### **Renal Cell Carcinoma (RCC) †**

- Patient must have metastatic or relapsed disease; **AND**
  - Must be used in combination with interferon alfa as first-line therapy for clear cell histology †; **OR**
  - Must be used as a single agent or 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 papillary disease including hereditary leiomyomatosis and renal cell cancer (HLRCC) ‡

### **Central Nervous System (CNS) Cancer**

- 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 ‡:
    - Supratentorial Astrocytoma/Oligodendroglioma (Low-Grade Infiltrative, WHO Grade II); **OR**
    - Primary CNS Lymphoma; **OR**
    - Meningiomas; **OR**
    - Brain, Spine, or Leptomeningeal metastases; **OR**
    - Medulloblastoma; **OR**
    - Recurrent Glioblastoma or Anaplastic Gliomas; **OR**
    - Recurrent Intracranial or Spinal Ependymoma (excluding subependymoma); **OR**
- Used as a single agent **OR** in combination with lomustine or temozolomide in patients with recurrent Glioblastomas † or Anaplastic Gliomas ‡; **OR**
- Used as single agent therapy for patients with progressive or recurrent disease who do not have subependymomas in patients with a diagnosis of recurrent Intracranial and Spinal Ependymoma ‡

### **Ovarian Cancer †**

- Patient has malignant stage II-IV sex cord-stromal tumors ‡; **AND**
  - Used as single agent therapy for relapsed disease; **OR**
- Patient has Epithelial or Fallopian Tube or Primary Peritoneal Cancers †; **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**
      - If platinum resistant, used in combination with one of the following: oral cyclophosphamide, PEGylated liposomal doxorubicin, weekly paclitaxel, or topotecan † or may be used as a single agent ‡; **OR**

- Used as neoadjuvant therapy for endometrioid or serous histology in combination with paclitaxel and carboplatin; **AND**
  - Patient has is a poor surgical candidate or has a low likelihood of optimal cytoreduction; **OR**
- Used as primary therapy for endometrioid or serous histology in combination with paclitaxel and carboplatin; **AND**
  - Patient had an incomplete resection and/or has unresectable stage II-IV residual disease; **OR**
- Used as adjuvant therapy in combination with paclitaxel and carboplatin; **AND**
  - Patient has stage II-IV disease of serous, endometrioid, mucinous carcinoma, or clear cell carcinoma histology; **OR**
  - Patient has borderline epithelial tumors with invasive implants; **OR**
- Used in combination with paclitaxel and carboplatin for patients with rising CA-125 levels or clinical relapse in patients with no prior chemotherapy.

#### **Soft Tissue Sarcoma †**

- Used as a single agent for angiosarcoma; **OR**
- Used in combination with temozolomide for solitary fibrous tumor or hemangiopericytoma

#### **Endometrial Carcinoma †**

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

#### **Malignant Pleural Mesothelioma †**

- Patient has unresectable or metastatic disease; **AND**
- Must be used first-line in combination with pemetrexed **AND** either cisplatin or carboplatin followed by single-agent maintenance bevacizumab

#### **AIDS-Related Kaposi Sarcoma †**

- Patient has relapsed or refractory disease; **AND**
- Patient has advanced cutaneous, oral, visceral, or nodal disease; **AND**
- Used as subsequent therapy in combination with antiretroviral therapy (ART) after failure to two lines of systemic therapy

#### **Vulvar Cancer †**

- Used in combination with paclitaxel and cisplatin for squamous cell carcinoma; **AND**
- Patient has unresectable locally advanced, metastatic, or recurrent 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)

Genomic Aberration Targeted Therapies ( <i>not all inclusive</i> ) §
Sensitizing EGFR mutation-positive tumors <ul style="list-style-type: none"> <li>- Erlotinib</li> <li>- Afatinib</li> <li>- Gefitinib</li> <li>- Dacomitinib</li> <li>- Osimertinib</li> </ul>
ALK rearrangement-positive tumors <ul style="list-style-type: none"> <li>- Crizotinib</li> <li>- Ceritinib</li> <li>- Brigatinib</li> <li>- Alectinib</li> </ul>
ROS1 rearrangement-positive tumors <ul style="list-style-type: none"> <li>- Crizotinib</li> <li>- Ceritinib</li> </ul>
BRAF V600E-mutation positive tumors <ul style="list-style-type: none"> <li>- Dabrafenib/Trametinib</li> </ul>
PD-L1 expression-positive tumors (>1%) <ul style="list-style-type: none"> <li>- Pembrolizumab</li> <li>- Atezolizumab</li> </ul>

#### IV. Renewal Criteria

Coverage can be renewed based upon the following criteria:

- Patient continues to meet the criteria identified in section III; **AND**
- Tumor response with 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 perforation, surgical/wound healing complications, hemorrhage, arterial and venous thromboembolic events (ATE & VTE), uncontrolled hypertension, posterior reversible encephalopathy syndrome (PRES), nephrotic syndrome, severe infusion reactions, ovarian failure, congestive heart failure (CHF), etc.; **AND**

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

- May NOT be renewed

#### **Colorectal Cancer (additional renewal opportunity):**

- Patient’s disease has progressed on a first-line bevacizumab-containing regimen; **AND**
  - Used in combination with an irinotecan and/or oxaliplatin-based regimen (if not used first line)

#### **Malignant Pleural Mesothelioma – maintenance therapy:**

- Must be used as a single agent

#### **Non-squamous non-small cell lung cancer – continuation maintenance therapy:**

- Bevacizumab must have been included in patient’s 1<sup>st</sup> line chemotherapy; **AND**
- Patient must have an ECOG performance status  $\leq 2$ ; **AND**
  - Used as a single agent; **OR**
  - Used as a single agent or in combination with atezolizumab if bevacizumab was previously used first-line as part of atezolizumab/carboplatin/paclitaxel/bevacizumab regimen

## V. Dosage/Administration

Indication	Dose
CRC	5 to 10 mg/kg every 2 weeks or 7.5 mg/kg every 3 weeks
NSCLC & Cervical Cancer	15 mg/kg every 3 weeks until disease progression or unacceptable toxicity.
CNS Cancers	–For disease treatment: 10 mg/kg every 2 weeks until disease progression or unacceptable toxicity. –For symptom management: 5-10 mg/kg every 2 weeks up to 12 weeks duration
RCC	10 mg/kg every 2 weeks until disease progression or unacceptable toxicity.
MPM	15 mg/kg every 3 weeks in combination with chemotherapy for up to 6 cycles followed by single agent use, at the same dose/frequency, until disease progression or unacceptable toxicity.
Ovarian Cancer	<u>Platinum-resistant</u> : 10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks until disease progression or unacceptable toxicity
All Other Oncology Indications	5-10 mg/kg every 2 weeks <b>OR</b> 7.5-15 mg/kg every 3 weeks

## VI. Billing Code/Availability Information

### Jcode:

- J9035 – Injection, bevacizumab, 10 mg; 1 billable unit = 10 mg

### NDC:

- 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

## VII. References

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## Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
C17.0	Malignant neoplasm duodenum
C17.1	Malignant neoplasm jejunum
C17.2	Malignant neoplasm ileum
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

ICD-10	ICD-10 Description
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
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
C46.0	Kaposi's sarcoma of skin
C46.1	Kaposi's sarcoma of soft tissue
C46.2	Kaposi's sarcoma of palate
C46.3	Kaposi's sarcoma of lymph nodes
C46.4	Kaposi's sarcoma of gastrointestinal sites
C46.50	Kaposi's sarcoma of unspecified lung
C46.51	Kaposi's sarcoma of right lung
C46.52	Kaposi's sarcoma of left lung
C46.7	Kaposi's sarcoma of other sites
C46.9	Kaposi's sarcoma, unspecified
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

ICD-10	ICD-10 Description
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
C51.0	Malignant neoplasm of labium majus
C51.1	Malignant neoplasm of labium minus
C51.2	Malignant neoplasm of clitoris
C51.8	Malignant neoplasm of overlapping sites of vulva
C51.9	Malignant neoplasm of vulva, 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
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

ICD-10	ICD-10 Description
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
C79.31	Secondary malignant neoplasm of brain
C79.32	Secondary malignant neoplasm of cerebral meninges
C79.82	Secondary malignant neoplasm of genital organs
C79.89	Secondary malignant neoplasm of other specified sites
C79.9	Secondary malignant neoplasm of unspecified site
C83.30	Diffuse large B-cell lymphoma unspecified site
C83.31	Diffuse large B-cell lymphoma lymph nodes of head, face, and neck
C83.39	Diffuse large B-cell lymphoma extranodal and solid organ sites
C83.80	Other non-follicular lymphoma unspecified site
C83.81	Other non-follicular lymphoma lymph nodes of head, face, and neck

ICD-10	ICD-10 Description
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
Z85.528	Personal history of other malignant neoplasm of kidney
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) and Local Coverage Determinations (LCDs) 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):

<b>Jurisdiction(s):</b> 6, K	<b>NCD/LCD Document (s):</b> A52370
<a href="https://www.cms.gov/medicare-coverage-database/search/article-date-search.aspx?DocID=A52370&amp;bc=gAAAAAAAAAAAAA">https://www.cms.gov/medicare-coverage-database/search/article-date-search.aspx?DocID=A52370&amp;bc=gAAAAAAAAAAAAA</a> ==	

<b>Jurisdiction(s):</b> 15
<a href="https://www.cms.gov/medicare-coverage-database/details/article-details.aspx?articleId=56604&amp;ver=2&amp;DocID=A56604&amp;bc=gAAAABAAAA&amp;">https://www.cms.gov/medicare-coverage-database/details/article-details.aspx?articleId=56604&amp;ver=2&amp;DocID=A56604&amp;bc=gAAAABAAAA&amp;</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)



**Medicare Part B Administrative Contractor (MAC) Jurisdictions**

<b>Jurisdiction</b>	<b>Applicable State/US Territory</b>	<b>Contractor</b>
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	<a href="#">Phase 3 (Study AVF2107)</a> , randomized, double-blind, active-controlled	IFL + placebo	OS	First-line	<ul style="list-style-type: none"> <li>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</li> </ul>
Bevacizumab + FOLFOX	2A	Yes	<a href="#">Phase 2 (TREE study)</a> , randomized, open-label	Bevacizumab + bFOL (bolus FU, LV, oxaliplatin) vs. bevacizumab + CapeOX	Incidence of grade 3/4 AEs	First-line	<ul style="list-style-type: none"> <li>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.</li> <li>First-line oxaliplatin and fluoropyrimidine-based therapy plus bevacizumab resulted in a median OS of approximately 2 years.</li> </ul>
Bevacizumab + FOLFOX or XELOX	2A	Yes	<a href="#">Phase 3 (N016966)</a> , randomized	Placebo + FOLFOX or XELOX	PFS	First-line	<ul style="list-style-type: none"> <li>The addition of bevacizumab to oxaliplatin-based chemotherapy significantly improved PFS in this first-line trial in patients with mCRC</li> </ul>

							<ul style="list-style-type: none"> <li>Overall survival differences did not reach statistical significance, and response rate was not improved by the addition of bevacizumab.</li> </ul>
Bevacizumab + FOLFOXIRI	2A	Yes	<a href="#">Phase 3 (TRIBE)</a> , randomized, open-label, multi-center  <a href="#">Updated analysis</a>	Bevacizumab + FOLFIRI	PFS	First-line	<ul style="list-style-type: none"> <li>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</li> </ul>
Bevacizumab + capecitabine			<a href="#">Phase 3 (AVEX)</a> , open-label, randomized	Capecitabine	PFS	First-line	<ul style="list-style-type: none"> <li>The combination of bevacizumab and capecitabine demonstrated a significant improvement in PFS and was well-tolerated in elderly patients with metastatic colorectal cancer</li> </ul>
Bevacizumab + FU + LV			<a href="#">Phase 2</a> , randomized	FU + LV + placebo	OS	First-line	<ul style="list-style-type: none"> <li>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.</li> </ul>
Cetuximab + FOLFIRI	2A (for KRAS/ NRAS WT and left-sided tumors only)	Yes	<a href="#">Phase 3 (CRYSTAL)</a> , randomized, open-label, multi-center  <a href="#">Updated analysis</a>	FOLFIRI	PFS	First-line	<ul style="list-style-type: none"> <li>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 limited to patients with KRAS wild-type tumors.</li> </ul>

Cetuximab + FOLFOX	2A (for KRAS/ NRAS WT and left-sided tumors only)		<a href="#">Phase 3 (TAILOR)</a> , open-label, randomized	FOLFOX	PFS	First-line	<ul style="list-style-type: none"> <li>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.</li> </ul>
Panitumumab + FOLFOX	2A (for KRAS/ NRAS WT and left-sided tumors only)	Yes	<a href="#">Phase 3 (PRIME)</a> , randomized, open-label  <a href="#">Final results</a>	FOLFOX	PFS	First-line	<ul style="list-style-type: none"> <li>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</li> </ul>
Panitumumab+ FOLFIRI	2A (for KRAS/ NRAS WT and left-sided tumors only)	No	<a href="#">Phase 2</a> , single-arm	N/A	-----	First-line	<ul style="list-style-type: none"> <li>A favorable efficacy (ORR 56%) was observed in patients with KRAS wild-type CRC receiving first-line panitumumab plus FOLFIRI treatment.</li> </ul>
Bevacizumab + FOLFIRI	2A	Yes	<a href="#">Phase 3 (FIRE-3)</a> , randomized, open-label  <a href="#">Primary tumor location analysis</a>	Cetuximab + FOLFIRI	ORR	First-line	<ul style="list-style-type: none"> <li>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.</li> <li>More benefit was shown for cetuximab in left-sided tumors than bevacizumab.</li> </ul>
Bevacizumab + FOLFOX or FOLFIRI	2A	Yes	<a href="#">Phase 3 (CALGB/ SWOG)</a> , randomized	Cetuximab + FOLFOX or FOLFIRI	OS	First-line	<ul style="list-style-type: none"> <li>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.</li> </ul>

			<a href="#">Retrospective re-analysis – Impact of primary tumor location</a>				<ul style="list-style-type: none"> <li>In KRAS wild type mCRC, patients with left-sided primary tumor have superior OS and PFS versus patients with right-sided primary tumor.</li> </ul>
Panitumumab + FOLFOX	2A (for KRAS/ NRAS WT and left-sided tumors only)	Yes	<a href="#">Phase 2 (PEAK)</a> , randomized, multi-center	Bevacizumab + FOLFOX	PFS	First-line	<ul style="list-style-type: none"> <li>PFS was similar and OS was improved with panitumumab relative to bevacizumab when combined with FOLFOX in patients with wild-type KRAS tumors.</li> </ul>
Bevacizumab-containing regimen	2A	Yes	<a href="#">Retrospective meta-analysis of FIRE-3, CALGB/ SWOG 80405, &amp; PEAK</a>	Erbix or Vectibix-containing regimens	-----	First-line	<ul style="list-style-type: none"> <li>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</li> <li>Avastin was associated with a longer survival in patients with right-sided CRC</li> </ul>

**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-based chemotherapy including either irinotecan or oxaliplatin	2A	Yes	<a href="#">Phase 3 (TML study)</a> , prospective, randomized, open-label, multinational, controlled	Fluoropyrimidine-based chemotherapy including either irinotecan or oxaliplatin	OS	Previous treatment with bev + fluoropyrimidine and either oxaliplatin or irinotecan	<ul style="list-style-type: none"> <li>Maintenance of VEGF inhibition with bevacizumab plus standard second-line chemotherapy beyond disease progression has clinical benefits in OS and PFS in patients with metastatic colorectal cancer. Treatment effects were independent of KRAS mutation status.</li> </ul>

**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	<a href="#">Phase 3 (Study E3200)</a> , open-label, randomized, active-controlled, multicenter	5-fluorouracil (5-FU) + leucovorin + oxaliplatin (FOLFOX4)	OS	Second-line	<ul style="list-style-type: none"> <li>The addition of bevacizumab to oxaliplatin, fluorouracil, and leucovorin improves survival duration for patients with previously treated metastatic colorectal cancer</li> </ul>
Bevacizumab + FOLFIRI	2A (preferred after previous oxaliplatin- or fluoropyrimidine-based therapy without irinotecan or oxaliplatin)	Yes	<a href="#">Phase 2 (SPIRITT)</a> , randomized, multi-center	Panitumumab + FOLFIRI	PFS	Second-line after oxaliplatin-based therapy plus bevacizumab	<ul style="list-style-type: none"> <li>Panitumumab or bevacizumab with FOLFIRI as second-line treatment had efficacy similar in patients whose disease progressed during oxaliplatin-based chemotherapy with bevacizumab</li> </ul>
Panitumumab	2A	No	<a href="#">Phase 3</a> , open-label, randomized  <a href="#">Retrospective analysis</a>	Best supportive care (BSC)	PFS	After disease progression on oxaliplatin/irinotecan-based chemotherapy	<ul style="list-style-type: none"> <li>Panitumumab monotherapy efficacy in mCRC is confined to patients with WT KRAS tumors</li> </ul>
Panitumumab	2A	Yes	<a href="#">Phase 3</a> , randomized	Best supportive care (BSC)	OS	After disease progression on oxaliplatin/irinotecan-based chemotherapy	<ul style="list-style-type: none"> <li>Panitumumab significantly improved OS in wild-type KRAS exon 2 mCRC.</li> </ul>

Panitumumab + FOLFIRI	2A	Yes	<a href="#">Phase 3 (Study 181)</a> , randomized	FOLFIRI	PFS OS	Second-line	<ul style="list-style-type: none"> <li>• Panitumumab plus FOLFIRI significantly improved PFS, however the improvement in OS was nonsignificant</li> </ul>
Cetuximab + irinotecan	2A	Yes	<a href="#">Phase 3 (EPIC)</a> , multi-center, open-label	Irinotecan	OS	After fluoropyrimidine and oxaliplatin	<ul style="list-style-type: none"> <li>• Cetuximab and irinotecan improved PFS and ORR versus irinotecan alone. OS was similar between study groups</li> </ul>
Panitumumab	2A	No	<a href="#">Phase 3 (ASPECCT)</a> , randomized, multi-center, open-label, non-inferiority	Cetuximab	Non-inferiority OS	Chemo-refractory	<ul style="list-style-type: none"> <li>• Panitumumab is non-inferior to cetuximab. These agents provide similar overall survival benefit in patients with KRAS wild type mCRC.</li> </ul>
Ziv-Aflibercept+ FOLFIRI	2A (after regimen NOT containing irinotecan)		<a href="#">Phase 3 (VELOUR)</a> , randomized  <a href="#">Subgroup analysis</a>	FOLFIRI + placebo	OS	Second-line after oxaliplatin-based regimen	<ul style="list-style-type: none"> <li>• Aflibercept in combination with FOLFIRI conferred a statistically significant survival benefit over FOLFIRI combined with placebo in patients with mCRC previously treated with oxaliplatin</li> <li>• Benefit in OS was also shown in patients with prior bevacizumab treatment</li> </ul>
Ramucirumab +FOLFIRI	2A (after regimen NOT containing irinotecan)	Yes	<a href="#">Phase 3 (RAISE)</a> , randomized, double-blind, multi-center	FOLFIRI + placebo	OS	After first-line fluoro + oxali + bev	<ul style="list-style-type: none"> <li>• Ramucirumab plus FOLFIRI significantly improved overall survival compared with placebo plus FOLFIRI as second-line treatment for patients with metastatic colorectal carcinoma</li> </ul>
Pembrolizumab	2A	Yes	<a href="#">Phase 2</a>	N/A	ORR PFS rate	After 2-4 previous therapies	<ul style="list-style-type: none"> <li>• Mismatch-repair status predicted clinical benefit of immune checkpoint blockade with pembrolizumab in patients with CRC</li> </ul>

Nivolumab +/- ipilimumab	2A	Yes	<a href="#">Phase 2 (CheckMate-142)</a> , open-label, multi-center	N/A	ORR	Second-line or later	<ul style="list-style-type: none"> <li>Nivolumab provided durable responses and disease control in pre-treated patients with dMMR/MSI-H metastatic colorectal cancer</li> </ul>
Bevacizumab + FOLFIRI or FOLFOX	2A	Yes	<a href="#">Phase 2 (PRODIGE 18)</a> , randomized	Erbitux + FOLFIRI or FOLFOX	PFS	Second-line after Avastin chemotherapy	<ul style="list-style-type: none"> <li>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.</li> </ul>

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

First-Line Therapy of Recurrent, Locally 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 adenocarcinoma only; PS 0-1)	Yes	<a href="#">Phase 2/3 (ECOG 4599)</a> , randomized	Carboplatin + paclitaxel	OS	First-line	<ul style="list-style-type: none"> <li>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</li> </ul>
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	<a href="#">Phase 3 (KEYNOTE-024)</a> , open-label, randomized	Platinum-based chemotherapy	PFS	First-line	<ul style="list-style-type: none"> <li>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</li> </ul>
<b>First-Line Therapy of Recurrent, Advanced, or Metastatic Disease - EGFR, ALK negative or unknown, regardless of PD-L1 expression</b>							
Regimen	NCCN Category	FDA Approved	Trial Design	Comparator	Primary End-Point	Line of Therapy	Conclusion
Atezolizumab + carboplatin + paclitaxel + bevacizumab (ABCP)	1 (for adenocarcinoma only; PS 0-1)	Yes	<a href="#">Phase 3 (IMpower150)</a> , open-label, randomized (1:1:1)	Atezolizumab + carboplatin + paclitaxel (ACP) vs. bevacizumab + carboplatin + paclitaxel (BCP)	PFS	First-line	<ul style="list-style-type: none"> <li>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</li> </ul>
Pembrolizumab + carboplatin (or cisplatin) + pemetrexed	1 preferred (for adenocarcinoma only; PS 0-1)	Yes	<a href="#">Phase 3 (KEYNOTE-189)</a> , double-blind, randomized (2:1)	Carboplatin (or cisplatin) + pemetrexed + placebo	OS PFS	First-line	<ul style="list-style-type: none"> <li>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</li> </ul>
Carboplatin + docetaxel (DCb) or Cisplatin + docetaxel (DC)	1 (for PS 0-1) 2A (for PS 2)	No	<a href="#">Phase 3 (TAX326)</a> , randomized, multinational	Cisplatin + vinorelbine (VC)	-----	First-line	<ul style="list-style-type: none"> <li>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</li> </ul>

							therapeutic index for first-line treatment of advanced or metastatic /NSCLC.
Carboplatin + paclitaxel (TC)	1 (for PS 0-1) 2A (for PS 2)	No	<a href="#">Phase 3</a> , randomized	Cisplatin + irinotecan (IP) vs. cisplatin + gemcitabine (GP) vs. cisplatin + vinorelbine (NP)	OS	First-line	<ul style="list-style-type: none"> <li>The four regimens have similar efficacy and different toxicity profiles, and they can be used to treat advanced NSCLC patients.</li> </ul>
Cisplatin + etoposide	1 (for PS 0-1)	No	<a href="#">Phase 3</a> , randomized	Cisplatin + gemcitabine	ORR	First-line	<ul style="list-style-type: none"> <li>Compared with etoposide-cisplatin, gemcitabine-cisplatin provides a significantly higher response rate and a delay in disease progression</li> </ul>
Bevacizumab + cisplatin + gemcitabine	None	No	<a href="#">Phase 3 (AVAiL)</a> , randomized	Cisplatin + gemcitabine + placebo (CG)	PFS	First-line	<ul style="list-style-type: none"> <li>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.</li> </ul>

**Recurrent, Advanced, or Metastatic Disease**

<b>Regimen</b>	<b>NCCN Category</b>	<b>FDA Approved</b>	<b>Trial Design</b>	<b>Comparator</b>	<b>Primary End-Point</b>	<b>Line of Therapy</b>	<b>Conclusion</b>
Bevacizumab + carboplatin + pemetrexed, followed by pemetrexed +	2A (for adenocarcinoma only; PS 0-1)	No	<a href="#">Phase 3 (PointBreak)</a> , randomized	Bevacizumab + carboplatin + paclitaxel, followed by bevacizumab (PacCBev)	OS	First-line	<ul style="list-style-type: none"> <li>OS did not improve with the PemCBev regimen compared with the PacCBev regimen, although PFS was significantly improved with PemCBev</li> </ul>

bevacizumab (PemCBev)							
Bevacizumab + cisplatin + pemetrexed followed by bevacizumab maintenance	2A (for adenocarcinoma only; PS 0-1)	No	<a href="#">Phase 3 (AVAPERL [MO22089])</a> , randomized	Bevacizumab + cisplatin + pemetrexed followed by bevacizumab + pemetrexed maintenance	PFS	First-line	<ul style="list-style-type: none"> <li>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</li> </ul>
<b>Continuation Maintenance Therapy</b>							
<b>Regimen</b>	<b>NCCN Category</b>	<b>FDA Approved</b>	<b>Trial Design</b>	<b>Comparator</b>	<b>Primary End-Point</b>	<b>Line of Therapy</b>	<b>Conclusion</b>
Bevacizumab monotherapy (Bevacizumab + carboplatin + paclitaxel, followed by maintenance therapy with bevacizumab)	1 (if previously given)	No	<a href="#">Phase 2/3 (ECOG 4599)</a> , randomized	Carboplatin + paclitaxel, followed by no maintenance therapy	OS	First-line	<ul style="list-style-type: none"> <li>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</li> </ul>
Bevacizumab + atezolizumab (Atezolizumab + carboplatin + paclitaxel + bevacizumab, followed by maintenance therapy with atezolizumab +	1 (if previously given)	No	<a href="#">Phase 3 (IMpower150)</a> , open-label, randomized (1:1:1)	Atezolizumab + carboplatin + paclitaxel, followed by atezolizumab (ACP) vs. bevacizumab + carboplatin + paclitaxel, followed by	PFS	First-line	<ul style="list-style-type: none"> <li>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</li> </ul>

bevacizumab [ABCP])				bevacizumab (BCP)			
Bevacizumab + pemetrexed (Bevacizumab + carboplatin + pemetrexed, followed by pemetrexed + bevacizumab [PemCBev])	2A (if previously given)	No	<a href="#">Phase 3 (PointBreak)</a> , randomized	Bevacizumab + carboplatin + paclitaxel, followed by bevacizumab (PacCBev)	OS	First-line	<ul style="list-style-type: none"> <li>OS did not improve with the PemCBev regimen compared with the PacCBev regimen, although PFS was significantly improved with PemCBev</li> </ul>
Bevacizumab + cisplatin + pemetrexed followed by bevacizumab maintenance	2A (if previously given)	No	<a href="#">Phase 3 (AVAPERL [MO22089])</a> , randomized	Bevacizumab + cisplatin + pemetrexed followed by bevacizumab + pemetrexed maintenance	PFS	First-line	<ul style="list-style-type: none"> <li>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</li> </ul>
<b>Subsequent Therapy</b>							
<b>Regimen</b>	<b>NCCN Category</b>	<b>FDA Approved</b>	<b>Trial Design</b>	<b>Comparator</b>	<b>Primary End-Point</b>	<b>Line of Therapy</b>	<b>Conclusion</b>
Bevacizumab + standard-of-care (Bev + SOC)	2A	No	<a href="#">Phase 3b (AvaALL)</a> , 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	<ul style="list-style-type: none"> <li>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.</li> </ul>

						bevacizumab maintenance	
Nivolumab	1 (for first progression)  2A (for subsequent progression)	Yes	<a href="#">Phase 3 (CheckMate 057)</a> , randomized, open-label	Docetaxel	OS	Subsequent	<ul style="list-style-type: none"> <li>Among patients with advanced nonsquamous NSCLC that had progressed during or after platinum-based chemotherapy, overall survival was longer with nivolumab than with docetaxel</li> </ul>
Pembrolizumab (2mg/kg or 10mg/kg)	1 preferred (for PS 0-2; PD-L1 ≥ 1%)	Yes (after platinum therapy)	<a href="#">Phase 2/3 (KEYNOTE-010)</a> , randomized (1:1:1), open-label	Docetaxel	OS PFS	Previously treated	<ul style="list-style-type: none"> <li>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.</li> </ul>
Atezolizumab	1 (for first progression)  2A (for subsequent progression)	Yes (after platinum therapy)	<a href="#">Phase 3 (OAK)</a> , open-label, multicenter randomized (1:1)	Docetaxel	OS	Second- or third-line	<ul style="list-style-type: none"> <li>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</li> </ul>
Ramucirumab + docetaxel	2A (first progression only)	Yes (after platinum therapy)	<a href="#">Phase 3 (REVEL)</a> , multicenter, double-blind, randomized (1:1)	Docetaxel + placebo	OS	Second-line after platinum-based regimen	<ul style="list-style-type: none"> <li>Ramucirumab plus docetaxel improves survival as second-line treatment of patients with stage IV NSCLC</li> </ul>

## 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	<a href="#">Phase 3 (GOG-0240)</a> , randomized, controlled, open-label	Cisplatin + paclitaxel vs. topotecan + paclitaxel +/- bevacizumab vs. topotecan + paclitaxel	OS	Recurrent or persistent disease	<ul style="list-style-type: none"> <li>• Bevacizumab improved survival in patients with advanced cervical cancer with by 3.5 months compared to chemotherapy alone.</li> </ul>
Cisplatin + paclitaxel (TP)	1 preferred		<a href="#">Phase 3 (GOG 169)</a> , randomized	Cisplatin	ORR PFS OS	First-line	<ul style="list-style-type: none"> <li>• Combination therapy with cisplatin and paclitaxel is superior to cisplatin alone with respect to response rate and PFS.</li> </ul>
Cisplatin + paclitaxel (TP)	1 preferred	No	<a href="#">Phase 3 (JCOG0505)</a> , 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 preferred	Yes	See data for bevacizumab + cisplatin + paclitaxel; <a href="#">Phase 3 (GOG-0240)</a>				
Carboplatin + paclitaxel	1 preferred (for patients who have received prior cisplatin therapy)	No	See data for cisplatin + paclitaxel; <a href="#">Phase 3 (JCOG0505)</a>				

Bevacizumab + carboplatin + paclitaxel	2A preferred	No	See data for bevacizumab + cisplatin + paclitaxel; <a href="#">Phase 3 (GOG-0240)</a> See data for cisplatin + paclitaxel; <a href="#">Phase 3 (JCOG0505)</a>
Topotecan + paclitaxel	2A preferred	No	See data for bevacizumab + cisplatin + paclitaxel; <a href="#">Phase 3 (GOG-0240)</a>

### Second-line Therapy

Regimen	NCCN Category	FDA Approved	Trial Design	Comparator	Primary End-Point	Line of Therapy	Conclusion
Bevacizumab	2B	No	<a href="#">Phase 2</a>	N/A	6-mon PFS	Second- or third-line	<ul style="list-style-type: none"> <li>Bevacizumab is active in second- and third-line treatment with an ORR of 11%</li> </ul>
Pembrolizumab	2A preferred (for MSI-H /dMMR or PD-L1 positive tumors)	Yes (for PD-L1 positive tumors)	<a href="#">Phase 2 (KEYNOTE-158)</a> , multi-center, open-label, multi-cohort	N/A	ORR	Second-line or later	<ul style="list-style-type: none"> <li>Pembrolizumab demonstrated anti-tumor activity with an ORR of 16% PD-L1 expressing refractory cervical cancer</li> </ul>

### 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	<a href="#">Phase 3 (E2100)</a> , open-label, randomized	Paclitaxel (T)	PFS	First-line	<ul style="list-style-type: none"> <li>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</li> </ul>

Bevacizumab + chemotherapy (capecitabine, taxane, or anthracycline)	2A	No	<a href="#">Phase 3 (RIBBON-1)</a> , randomized, double-blind, placebo-controlled	Chemotherapy + placebo	PFS	First-line	<ul style="list-style-type: none"> <li>The combination of BV with Cape, Tax, or Anthra 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.</li> </ul>
Bevacizumab + docetaxel	None	No	<a href="#">Phase 3 (AVADO)</a> , randomized, double-blind	Docetaxel + placebo	PFS	First-line	<ul style="list-style-type: none"> <li>Bevacizumab 15 mg/kg every 3 weeks increased PFS when combined with docetaxel as first-line therapy for MBC compared with docetaxel plus placebo.</li> </ul>
Doxorubicin + cyclophosphamide (AC)	2A	No	<a href="#">Phase 3</a> , randomized, multi-center	Doxorubicin + docetaxel (AT)	TTP	First-line	<ul style="list-style-type: none"> <li>AT significantly improves TTP and ORR compared with AC in patients with MBC, but there is no difference in OS</li> </ul>
Epirubicin + cyclophosphamide (EC)	2A	No	<a href="#">Phase 3 (AB01)</a> , randomized, multi-center	Epirubicin + paclitaxel (EP)	PFS	First-line	<ul style="list-style-type: none"> <li>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.</li> </ul>
Docetaxel + capecitabine (DC)	2A	No	<a href="#">Phase 3</a> , randomized, multi-center	Docetaxel + epirubicin (DE)	TTP	First-line	<ul style="list-style-type: none"> <li>The DE and DC regimens have similar efficacy but different toxicity. Either regimen can be used as front-line treatment of ABC.</li> </ul>
Gemcitabine + paclitaxel (GT)	2A	No	<a href="#">Phase 3</a> , randomized	Paclitaxel (T)	OS	First-line (after adjuvant anthracycline)	<ul style="list-style-type: none"> <li>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.</li> </ul>



Nab-paclitaxel + bevacizumab	2A	Yes	<a href="#">Phase 3</a> , randomized	Ixabepilone + bevacizumab vs. paclitaxel + bevacizumab	PFS	First-line	<ul style="list-style-type: none"> <li>• PFS and OS for nab-paclitaxel was not superior to paclitaxel with a trend toward inferiority</li> <li>• Toxicity was increased for nab-paclitaxel</li> </ul>
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## 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	1 for all risk groups	Yes	<a href="#">Phase 3 (AVOREN)</a> , multi-center, randomized, double-blind	Interferon-alfa (IFN- $\alpha$ ) + placebo	OS	First-line	<ul style="list-style-type: none"> <li>• 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.</li> </ul>
Bevacizumab + interferon alfa	1 for all risk groups	Yes	<a href="#">Phase 3 (CALGB 90206)</a> , randomized	IFN- $\alpha$	OS	First-line	<ul style="list-style-type: none"> <li>• 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.</li> </ul>
Pazopanib	1 preferred for favorable risk 1 for poor/intermediate risk	Yes	<a href="#">Phase 3 (VEG105192)</a> , open-label, double-blind, randomized, multi-center	Placebo	PFS	First-line or after cytokine therapy	<ul style="list-style-type: none"> <li>• 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.</li> </ul>

			<a href="#">Final OS results</a>				
Sunitinib	1 preferred for favorable risk  1 for poor/intermediate risk	Yes	<a href="#">Phase 3</a> , randomized, multi-center	IFN-α	PFS	First-line	<ul style="list-style-type: none"> <li>• PFS and ORR were both significantly longer/ higher with sunitinib than IFN-α.</li> <li>• A trend towards OS advantage of sunitinib over IFN-α was demonstrated.</li> </ul>
Nivolumab + ipilimumab	1 preferred for intermediate/poor-risk  2A for favorable risk	Yes for intermediate/poor-risk	<a href="#">Phase 3 (CheckMate 214)</a> , open-label, multi-center	Sunitinib	ORR PFS OS	First-line	<ul style="list-style-type: none"> <li>• 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.</li> </ul>
Nivolumab + ipilimumab	1 preferred for intermediate/poor-risk  2A for favorable risk	Yes for intermediate/poor-risk	<a href="#">Phase 1 (CheckMate 016)</a>	N/A	Safety	All lines of therapy	<ul style="list-style-type: none"> <li>• Nivolumab plus ipilimumab demonstrated an ORR of 40.4% in patients of all risk-groups, including patients who received prior therapy.</li> </ul>
Temsirolimus	1 for poor risk	Yes	<a href="#">Phase 3 (Global ARCC)</a> , multi-center	IFN-α vs. temsirolimus + IFN-α	OS	First-line	<ul style="list-style-type: none"> <li>• As compared with interferon alfa, temsirolimus improved overall survival among patients with metastatic renal-cell carcinoma and a poor prognosis</li> </ul>
Cabozantinib	2A preferred for poor/intermediate risk	Yes	<a href="#">Phase 2 (CABOSUN)</a> , open-label, randomized	Sunitinib	PFS	First-line	<ul style="list-style-type: none"> <li>• 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.</li> </ul>

	2B for favorable risk						
<b>Subsequent therapy for relapsed or stage IV disease – clear cell histology</b>							
<b>Regimen</b>	<b>NCCN Category</b>	<b>FDA Approved</b>	<b>Trial Design</b>	<b>Comparator</b>	<b>Primary End-Point</b>	<b>Line of Therapy</b>	<b>Conclusion</b>
Bevacizumab	2B	No					
Nivolumab + ipilimumab	1 preferred	Yes					
Cabozantinib	1 preferred	Yes					
Axitinib	1	Yes					
Lenvatinib + everolimus	1	Yes					
<b>Relapsed or stage IV non-clear cell histology</b>							
<b>Regimen</b>	<b>NCCN Category</b>	<b>FDA Approved</b>	<b>Trial Design</b>	<b>Comparator</b>	<b>Primary End-Point</b>	<b>Line of Therapy</b>	<b>Conclusion</b>
Bevacizumab	2A	No	<a href="#">Phase 2</a>	N/A	12-mon PFS	First- or second-line	<ul style="list-style-type: none"> <li>• PFS with bevacizumab alone ranged from 6-25 months and suggest activity with minimal toxicity.</li> </ul>
Bevacizumab + everolimus	2A	No	<a href="#">Phase 2</a> , single-center	N/A	PFS	First-line	<ul style="list-style-type: none"> <li>• Tumors with significant papillary or chromophobe elements showed higher PFS and ORR than other histologies.</li> <li>• Subjects with other variants (medullary RCC and unclassified RCC without papillary features), achieved little or no benefit from everolimus plus bevacizumab.</li> </ul>

Sunitinib	2A preferred	Yes	<a href="#">Phase 2</a>	N/A	ORR	No prior sunitinib, sorafenib, or bevacizumab	<ul style="list-style-type: none"> <li>Clinical activity with sunitinib in non-clear cell RCC is supported by an ORR of 36% and PFS of 6.4 months.</li> </ul>
Sunitinib	2A preferred	Yes	<a href="#">Phase 2 (ASPEN)</a> , multi-center, open-label, randomized	Everolimus	PFS	First-line	<ul style="list-style-type: none"> <li>Sunitinib improved PFS compared with everolimus in patients with metastatic non-clear cell RCC.</li> </ul>
Bevacizumab + erlotinib	2A	No	<a href="#">Phase 2</a>	N/A	ORR	First- and second-line	<ul style="list-style-type: none"> <li>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).</li> </ul>
Temsirolimus	1 (for poor prognosis features) 2A (all others)	No	<a href="#">Retrospective analysis of phase 3 Global ARCC Trial</a>	N/A	-----	First-line	<ul style="list-style-type: none"> <li>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</li> </ul>

## CNS Cancer

Recurrent anaplastic glioma							
Regimen	NCCN Category	FDA Approved	Trial Design	Comparator	Primary End-Point	Line of Therapy	Conclusion
Bevacizumab + chemotherapy	2B	No	<a href="#">Retrospective analysis</a>	N/A	-----	Recurrent gliomas	<ul style="list-style-type: none"> <li>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.</li> </ul>

Bevacizumab	2A	No	<a href="#">Retrospective analysis</a>	N/A	PFS	Recurrent alkylator-refractory anaplastic oligodendroglioma	<ul style="list-style-type: none"> <li>• Bevacizumab demonstrated efficacy in patients with recurrent alkylator-refractory anaplastic oligodendroglioma</li> </ul>
Bevacizumab	2A	No	<a href="#">Retrospective analysis</a>	N/A	-----	Recurrent alkylator-refractory anaplastic astrocytoma	<ul style="list-style-type: none"> <li>• Bevacizumab demonstrated efficacy with a 6 month PFS rate of 60%.</li> </ul>
Bevacizumab + irinotecan	2A	No	<a href="#">Retrospective analysis</a>	N/A	-----	Recurrent oligodendroglioma	<ul style="list-style-type: none"> <li>• Bevacizumab plus irinotecan is clinically active with a 6-mon PFS rate of 42%</li> </ul>
Bevacizumab + irinotecan	2A	No	<a href="#">Phase 2</a>	N/A	-----	Recurrent grade III-IV glioma	<ul style="list-style-type: none"> <li>• 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%.</li> </ul>
Bevacizumab + fotemustine (not FDA approved, available in Europe)	2A	No	<a href="#">Phase 2</a>	N/A	ORR 6-mon PFS	Recurrent glioma	<ul style="list-style-type: none"> <li>• Combination of bevacizumab and fotemustine in recurrent gliomas resulted an ORR of 35%</li> </ul>
Temozolomide	2A	Yes (anaplastic astrocytoma after progression on nitrosourea)	<a href="#">Phase 2</a> , open-label, multi-center	N/A	6-mon PFS	First relapse of anaplastic astrocytoma or anaplastic mixed oligoastrocytoma	<ul style="list-style-type: none"> <li>• 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</li> </ul>

		and procarbazine)					
Carmustine + $\alpha$ -difluoromethylornithine (DFMO)	2A	No	<a href="#">Clinical trial</a>	N/A	-----	Recurrent anaplastic gliomas and glioblastomas	<ul style="list-style-type: none"> <li>• Carmustine + DFMO demonstration clinical activity with a partial response rate of 9.5% and stable disease in 47.6% in patients with anaplastic gliomas.</li> </ul>
Procarbazine + lomustine + vincristine (PCV)	2A	No	<a href="#">Phase 2</a>	N/A	-----	Recurrent low-grade oligodendrogliomas and oligoastrocytomas	<ul style="list-style-type: none"> <li>• Chemotherapy with PCV is effective in the treatment of recurrent low-grade oligodendrogliomas and oligoastrocytomas</li> </ul>
<b>Recurrent glioblastoma</b>							
<b>Regimen</b>	<b>NCCN Category</b>	<b>FDA Approved</b>	<b>Trial Design</b>	<b>Comparator</b>	<b>Primary End-Point</b>	<b>Line of Therapy</b>	<b>Conclusion</b>
Bevacizumab	2A	Yes	<a href="#">Phase 2 (AVF3708g, BRAIN study)</a> , multi-center, open-label, non-comparative	Bevacizumab (bev) + irinotecan (CPT)	6-mon PFS ORR	Recurrent GBM	<ul style="list-style-type: none"> <li>• Bevacizumab alone or in combination with irinotecan appeared to be better than historical control serious with a 6-mon PFS rate of 43-50%.</li> </ul>
Bevacizumab + lomustine (bev + CCNU)	2A	No	<a href="#">Phase 3 (EORTC 26101)</a> , multi-center, randomized, open-label	Lomustine	OS	Recurrent GBM	<ul style="list-style-type: none"> <li>• Treatment with bevacizumab plus lomustine prolonged PFS however did not confer a survival advantage over treatment with lomustine alone in patients with progressive GBM.</li> </ul>

Bevacizumab + lomustine (bev + CCNU)	2A	Yes	<a href="#">Phase 2 (BELOB)</a> , randomized, open-label, multi-center	Single-agent bevacizumab or lomustine	9-mon OS	Recurrent GBM	<ul style="list-style-type: none"> <li>• Bevacizumab plus lomustine demonstrated increased effectiveness with a 9 months OS rate of 63% compared to either agent alone. (However, a benefit in OS was not observed in the phase III EORTC 26101 trial).</li> </ul>
Bevacizumab	2A	Yes	<a href="#">Phase 2</a>	N/A	6-mon PFS	Recurrent GBM	<ul style="list-style-type: none"> <li>• Single-agent bevacizumab has clinical activity in patients with recurrent GBM with a PFS of 16 weeks and OS of 31 weeks</li> </ul>
Bevacizumab + irinotecan	2A	No	<a href="#">Phase 2</a>	N/A	-----	Recurrent GBM	<ul style="list-style-type: none"> <li>• Bevacizumab and irinotecan is an effective treatment for recurrent glioblastoma with a 6-mon PFS of 46% and 6-mon OS of 77%.</li> </ul>
Bevacizumab + fotemustine	2A	No	<a href="#">Phase 2</a>	N/A	ORR 6-mon PFS	Recurrent glioma	<ul style="list-style-type: none"> <li>• Combination of bevacizumab and fotemustine in recurrent gliomas resulted an ORR of 35%</li> </ul>
Temozolomide (TMZ)	2A	No	<a href="#">Phase 2</a> , randomized, multi-center, open-label	Procarbazine	6-mon PFS	First-relapse	<ul style="list-style-type: none"> <li>• Temozolomide is effective in the treatment of patients with recurrent glioblastoma with a 6-month PFS rate of 21%.</li> </ul>
Temozolomide (TMZ)	2A	No	<a href="#">Phase 2 (DIRECTOR trial)</a>	N/A	TTF	Rechallenge with TMZ at first-progression	<ul style="list-style-type: none"> <li>• Temozolomide rechallenge is a treatment option for MGMT promoter-methylated recurrent glioblastoma with a TTF of 3.2 months.</li> </ul>
Temozolomide (TMZ)	2A	No	<a href="#">Phase 2 (RESCUE)</a> , multi-center	N/A	-----	Recurrent glioma (after previous TMZ treatment)	<ul style="list-style-type: none"> <li>• Rechallenge with TMZ demonstrated a 6-month PFS rate between 23-36%.</li> </ul>

Temozolomide (TMZ)	2A	No	<a href="#">Retrospective study</a>	N/A	-----	Non-progressive disease at first MRI after completion of TMZ concurrent with and adjuvant to radiotherapy, a treatment-free interval (TFI) of at least 8 weeks and received TMZ rechallenge at the time of progression	<ul style="list-style-type: none"> <li>• TFI ≥5 months represents a predictor of retained TMZ sensitivity</li> </ul>
Lomustine (CCNU)	2A	Yes	See Phase 3 (EORTC 26101) above				
Carmustine (BCNU)	2A	Yes	<a href="#">Phase 2</a>	N/A	-----	Recurrent glioblastoma	<ul style="list-style-type: none"> <li>• Carmustine demonstrated a 6-month PFS rate of 17.5%</li> </ul>
Procarbazine + lomustine + vincristine (PCV)	2A	No	<a href="#">Retrospective cohort study</a>	Bevacizumab + irinotecan	-----	Second-line	<ul style="list-style-type: none"> <li>• Bevacizumab plus irinotecan had higher response rates, almost twice the OS, and a lower degree of toxicity in contrast to the PCV group.</li> </ul>
Procarbazine + lomustine + vincristine (PCV)	2A	No	<a href="#">Retrospective analysis</a>	N/A	-----	Recurrent glioblastoma	<ul style="list-style-type: none"> <li>• PCV indicated to be useful in patients with recurrent glioblastoma with a 6-month PFs rate of 38.4%.</li> </ul>
<b>Adult intracranial and spinal Ependymoma (excluding subependymoma)</b>							
<b>Regimen</b>	<b>NCCN Category</b>	<b>FDA Approved</b>	<b>Trial Design</b>	<b>Comparator</b>	<b>Primary End-Point</b>	<b>Line of Therapy</b>	<b>Conclusion</b>



Bevacizumab (alone or with cytotoxic chemotherapy)	2A	No	<a href="#">Retrospective analysis</a>	N/A	-----	Recurrent ependymoma	<ul style="list-style-type: none"> <li>Use of bevacizumab-containing regimens appears to delay tumor progression (TTP 6.4mon) and demonstrated a partial response rate of 75%</li> </ul>
Cisplatin	2A	No	<a href="#">Retrospective analysis</a>	Without cisplatin	-----	Recurrent ependymoma	<ul style="list-style-type: none"> <li>Cisplatin-based chemotherapy achieved a higher response rate, but did not prolong disease progression-free survival or OS compared to regimens without cisplatin</li> </ul>

**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	<a href="#">Retrospective review</a>	N/A	-----	Recurrent or progressive disease	<ul style="list-style-type: none"> <li>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.</li> </ul>
Bevacizumab	2A	No	<a href="#">Retrospective review</a>	N/A	-----	-----	<ul style="list-style-type: none"> <li>Patients treated with bevacizumab demonstrated a 6-month PFS rate of 43.8% with the best response being stable disease</li> </ul>

**Radiation necrosis**

Regimen	NCCN Category	FDA Approved	Trial Design	Comparator	Primary End-Point	Line of Therapy	Conclusion
Bevacizumab	2A	No	<a href="#">Retrospective analysis</a>	N/A	-----	For acute neurologic deterioration in patients with GBM	<ul style="list-style-type: none"> <li>Single agent bevacizumab improved function and quality of life in patients with glioblastoma</li> </ul>

Bevacizumab (Q 3 weeks for 4 doses)	2A	No	<a href="#">Phase 2</a> , randomized, double-blind, placebo-controlled	Saline	Change in edema volume on MRI at 6 weeks	Radiation necrosis	<ul style="list-style-type: none"> <li>• Bevacizumab demonstrated efficacy with a response in all 5 patients who received bevacizumab in the treatment of radiation necrosis</li> </ul>
Bevacizumab (5mg/kg Q 2 weeks for 4 cycles)	2A	No	<a href="#">Phase 2</a> , randomized, controlled, open-label, multi-center trial	Corticosteroid	2-month ORR	Radiation necrosis after nasopharyngeal cancer therapy	<ul style="list-style-type: none"> <li>• Compared with corticosteroids, bevacizumab offers improved symptomatic relief and radiographic response.</li> </ul>

## 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	<a href="#">Phase 2 (GOG 170-D)</a>	N/A	PFS ORR	Second- or third-line	<ul style="list-style-type: none"> <li>• Bevacizumab demonstrated to be clinically active (ORR 21%) in second- and third-line treatment of patients with epithelial ovarian cancer and primary peritoneal cancer.</li> </ul>
Topotecan	2A	Yes	<a href="#">Phase 3</a> , randomized, multicenter	Liposomal doxorubicin	-----	Second-line or later	<ul style="list-style-type: none"> <li>• Liposomal doxorubicin prolonged survival compared with topotecan in patients with recurrent and refractory epithelial ovarian cancer by almost 7 weeks</li> <li>• Survival benefit is pronounced in patients with platinum-sensitive disease</li> </ul>

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	<a href="#">Phase 3 (OCEANS)</a> , randomized, multicenter, blinded, placebo-controlled  <a href="#">Final analysis</a>	Carboplatin + gemcitabine + placebo	PFS	Second-line; recurrence after at least 6 months of first-line platinum-based therapy	<ul style="list-style-type: none"> <li>• Carboplatin, gemcitabine, plus bevacizumab followed by bevacizumab until progression resulted in a statistically significant improvement in PFS compared with carboplatin, gemcitabine, plus placebo</li> <li>• The final survival analysis did not show an increase in OS with the chemotherapy plus bevacizumab arm when compared with chemotherapy alone.</li> </ul>
Carboplatin + paclitaxel + bevacizumab, followed by bevacizumab until progression	2A preferred	Yes	<a href="#">Phase 3 (GOG-0213)</a> , multicenter, open-label, randomized	Carboplatin + paclitaxel	OS	Second-line or later; relapsing after 6 months of being treatment-free	<ul style="list-style-type: none"> <li>• 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</li> </ul>
Carboplatin + liposomal doxorubicin	2A preferred	Yes (progressed or recurred after platinum-based chemotherapy)	<a href="#">Phase 3 (CALYPSO)</a> , randomized, multicenter	Carboplatin + paclitaxel	PFS	Second- or third-line therapy with recurrence after more than 6 months since first- or second-line platinum-based therapy	<ul style="list-style-type: none"> <li>• Carboplatin + liposomal doxorubicin demonstrated superiority in PFS compared to carboplatin + paclitaxel.</li> </ul>
Carboplatin + liposomal doxorubicin +	2A preferred	No	<a href="#">Phase 3 (AGO-OVAR 2.21)</a> , randomized	Carboplatin + gemcitabine +	PFS	Recurrent disease after at least 6 months after first-line platinum-	<ul style="list-style-type: none"> <li>• 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</li> </ul>

bevacizumab (CD-BEV)				bevacizumab (CG-BEV)		based chemotherapy (50% had prior anti-angiogenic treatment)	associated with fewer serious adverse events.
<b>Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer – Platinum Resistant</b>							
<b>Regimen</b>	<b>NCCN Category</b>	<b>FDA Approved</b>	<b>Trial Design</b>	<b>Comparator</b>	<b>Primary End-Point</b>	<b>Line of Therapy</b>	<b>Conclusion</b>
Bevacizumab + chemotherapy (paclitaxel, liposomal doxorubicin, or topotecan)	2A preferred	Yes	<a href="#">Phase 3 (AURELIA)</a> , randomized, multi-center, open-label	Chemotherapy alone (paclitaxel, liposomal doxorubicin, or topotecan)	PFS	Platinum-resistant, recurrent disease (no more than 2 prior chemo regimens)	<ul style="list-style-type: none"> <li>Adding bevacizumab to chemotherapy statistically significantly improved PFS and ORR; the OS trend was not significant.</li> </ul>
Bevacizumab + oral cyclophosphamide	2A preferred	No	<a href="#">Retrospective review</a>	N/A	-----	Platinum-resistant disease	<ul style="list-style-type: none"> <li>Bevacizumab and cyclophosphamide demonstrated to be effective in heavily pretreated patients with recurrent ovarian carcinoma</li> </ul>
Bevacizumab + oral cyclophosphamide	2A preferred	No	<a href="#">Phase 2</a>	N/A	6-mon PFS	Platinum-resistant, recurrent disease (no more than 2 prior chemo regimens)	<ul style="list-style-type: none"> <li>The combination of bevacizumab and oral cyclophosphamide is active in recurrent ovarian cancer with a 6-month PFS rate of 56%.</li> </ul>
Docetaxel	2A	No	<a href="#">Phase 2</a>	N/A	-----	Second-line	<ul style="list-style-type: none"> <li>Docetaxel is active in paclitaxel-resistant ovarian and peritoneal cancer but, in view of significant hematologic toxicity</li> </ul>
Etoposide (oral)	2A	No	<a href="#">Phase 2</a>	N/A	-----	Second-line therapy	<ul style="list-style-type: none"> <li>Etoposide is active in platinum-sensitive ovarian cancer with an ORR of 26.8%</li> </ul>

Topotecan	2A	Yes	<a href="#">Phase 3</a> , randomized, multicenter	Liposomal doxorubicin	-----	Second-line or later	<ul style="list-style-type: none"> <li>• Liposomal doxorubicin prolonged survival compared with topotecan in patients with recurrent and refractory epithelial ovarian cancer by almost 7 weeks</li> <li>• Survival benefit is pronounced in patients with platinum-sensitive disease</li> </ul>
Topotecan weekly (Tw)	2A	Yes	<a href="#">Phase 2 (TOWER)</a> , randomized	Topotecan conventional 5-day therapy (Tc)	ORR	Second-line and later	<ul style="list-style-type: none"> <li>• Conventional dosing of topotecan was more effective than weekly dosing in terms of response. There was no difference in median PFS or median OS.</li> </ul>

**Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer – Primary or Adjuvant 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	<a href="#">Phase 3 (GOG-0218)</a> , double-blind, placebo-controlled, randomized  <a href="#">Subgroup analysis</a>	Carboplatin + paclitaxel intravenous	PFS	Newly diagnosed stage III or IV epithelial ovarian cancer following initial surgical resection	<ul style="list-style-type: none"> <li>• 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.</li> <li>• A subgroup analysis suggested that upfront therapy with bevacizumab, carboplatin, and paclitaxel may be beneficial in patients with ascites.</li> </ul>
Bevacizumab + paclitaxel + carboplatin intravenous (bevacizumab given upfront and as maintenance)	2A	Yes	<a href="#">Phase 3 (ICON7)</a> , randomized  <a href="#">Overall survival results</a>	Carboplatin + paclitaxel intravenous	PFS	After surgery; patients with high-risk early-stage disease (clear cell or grade 3 tumors) or advanced disease	<ul style="list-style-type: none"> <li>• 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.</li> </ul>

Cisplatin + paclitaxel (IV/IP)	2A		<a href="#">Phase 3 (GOG 172)</a> , randomized	Cisplatin + paclitaxel (IV)	PFS OS	First-line, optimally resected (< 1cm residual mass)	<ul style="list-style-type: none"> <li>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</li> </ul>
Paclitaxel + carboplatin	2A		<a href="#">Phase 3</a> , randomized, non-inferiority trial	Paclitaxel + cisplatin	-----	First-line, optimally resected (< 1cm residual mass)	<ul style="list-style-type: none"> <li>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</li> </ul>
Paclitaxel + carboplatin	2A		<a href="#">Phase 3 (MITO-2)</a> , randomized	Pegylated liposomal doxorubicin (PLD) + carboplatin	PFS	First-line	<ul style="list-style-type: none"> <li>Carboplatin/PLD was not superior to carboplatin/paclitaxel, which remains the standard first-line chemotherapy for advanced ovarian cancer.</li> </ul>
Docetaxel + carboplatin	2A		<a href="#">Phase 3</a> , randomized	Paclitaxel + carboplatin	PFS	First-line	<ul style="list-style-type: none"> <li>Docetaxel-carboplatin appears to be similar to paclitaxel-carboplatin in terms of progression-free survival and response</li> </ul>
Pegylated liposomal doxorubicin (PLD) + carboplatin	2A		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	2A	No	<a href="#">Phase 2 (GEICO 1205/NOVA TRIAL)</a>	Carboplatin + paclitaxel	ORR	Neoadjuvant	<ul style="list-style-type: none"> <li>Neoadjuvant therapy with bevacizumab improved surgical</li> </ul>

			randomized, open-label				feasibility in patients initially considered unresectable.
Cisplatin or carboplatin	None	No	<a href="#">Phase 3 (EORTC-NCIC)</a> , randomized	Primary debulking surgery	OS	Neoadjuvant therapy of stage IIIC or IV disease	<ul style="list-style-type: none"> <li>• 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</li> </ul>
Carboplatin + paclitaxel	2A	No	<a href="#">Phase 3 (JCOG0602)</a> , randomized	Primary debulking surgery	OS	Neoadjuvant therapy	<ul style="list-style-type: none"> <li>• Superiority of neoadjuvant chemotherapy or primary debulking surgery could not be confirmed.</li> </ul>

#### Relapsed sex cord-stromal tumors

Regimen	NCCN Category	FDA Approved	Trial Design	Comparator	Primary End-Point	Line of Therapy	Conclusion
Bevacizumab	2A	No	<a href="#">Retrospective review</a>	N/A	-----	Recurrent disease after cytotoxic chemotherapy	<ul style="list-style-type: none"> <li>• Bevacizumab demonstrated activity for the treatment of recurrent ovarian granulosa cell tumors with an ORR of 38%.</li> </ul>
Bevacizumab	2A	No	<a href="#">Phase 2 (GOG 251)</a>	N/A	ORR	Recurrent disease; No prior bevacizumab	<ul style="list-style-type: none"> <li>• Bevacizumab has activity in the treatment of recurrent sex cord-stromal tumors of the ovary with an ORR of 16.7%.</li> </ul>
Leuprolide acetate	2A (granulosa cell tumors only)	No	<a href="#">Small study</a>	N/A	-----	First- or second-line	<ul style="list-style-type: none"> <li>• Leuprolide acetate appears to have activity in patients with refractory ovarian granulosa cell tumor with an ORR of 40%.</li> </ul>

#### Soft Tissue Sarcoma

##### Angiosarcoma

Regimen	NCCN Category	FDA Approved	Trial Design	Comparator	Primary End-Point	Line of Therapy	Conclusion
Bevacizumab	2A	No	<a href="#">Phase 2</a> , open-label, multi-center	N/A	PFS	First- through fourth-line therapy	<ul style="list-style-type: none"> <li>• 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.</li> </ul>
Paclitaxel	2A	No	<a href="#">Phase 2 (ANGIOTAX)</a>	N/A	PFS	All lines of therapy	<ul style="list-style-type: none"> <li>• Paclitaxel demonstrated efficacy in patients with metastatic or unresectable angiosarcoma with a 2-month PFS rate of 74%.</li> </ul>
Docetaxel	2A	No	<a href="#">Phase 2</a> , multi-center	N/A	-----	Second-line	<ul style="list-style-type: none"> <li>• Docetaxel has activity in adult soft tissue sarcoma in second-line therapy with a 17% partial response rate.</li> </ul>
Vinorelbine	2A (for palliative therapy only)						<ul style="list-style-type: none"> <li>•</li> </ul>
Sorafenib	2A	No	<a href="#">Phase 2</a>	N/A	ORR	First- through fourth-line therapy	<ul style="list-style-type: none"> <li>• As a single agent, sorafenib has activity against angiosarcoma and minimal activity against other sarcomas.</li> </ul>
Sunitinib	2A	No	<a href="#">Phase 2</a> , open-label, multi-center	N/A	ORR	First- through third-line therapy	<ul style="list-style-type: none"> <li>• Sunitinib demonstrated evidence of response in patients with non-GIST sarcoma. Specific results for patients with angiosarcoma however was not noted.</li> </ul>
<b>Solitary Fibrous Tumor/Hemangiopericytoma</b>							
Regimen	NCCN Category	FDA Approved	Trial Design	Comparator	Primary End-Point	Line of Therapy	Conclusion



Bevacizumab + temozolomide	2A	No	<a href="#">Retrospective analysis</a>	N/A	-----	All lines of therapy	<ul style="list-style-type: none"> <li>• Combination therapy with temozolomide and bevacizumab is a clinically beneficial regimen with a 79% partial response rate.</li> </ul>
Sunitinib	2A	No	<a href="#">Retrospective analysis</a>	N/A	-----	All lines of therapy	<ul style="list-style-type: none"> <li>• Sunitinib demonstrated clinical activity in patients with solitary fibrous tumors with 3 patients achieving a partial response and 16 patients with stable disease.</li> </ul>
Sorafenib	2A	No	<a href="#">Subgroup analysis from a Phase 2</a>	N/A	-----	Second-line and later	<ul style="list-style-type: none"> <li>• Data suggested a potential efficacy of sorafenib with 2 out of 5 patients achieving 9 months of disease control.</li> </ul>
Pazopanib	2A	No	<a href="#">Retrospective analysis</a>	N/A	-----	First- and second-line	<ul style="list-style-type: none"> <li>• Pazopanib is an effective treatment option for recurrent or metastatic solitary fibrous tumor in first- and second-line settings with an ORR of 50%.</li> </ul>

## 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	<a href="#">Phase 2 (MITO Group END-2 trial)</a> , randomized	Carboplatin + paclitaxel	-----	First- and second-line	<ul style="list-style-type: none"> <li>• The addition of bevacizumab to carboplatin plus paclitaxel significantly increased PFS in advanced or recurrent endometrial cancer.</li> </ul>
Bevacizumab + carboplatin + paclitaxel	2A (for advanced or	No	<a href="#">Retrospective analysis</a>	N/A	-----	First- and second-line	<ul style="list-style-type: none"> <li>• Combination therapy with bevacizumab, paclitaxel, and carboplatin demonstrated an ORR of</li> </ul>

	recurrent disease only)						82.8%, PFS of 20 months, and OS of 56 months.
Carboplatin + paclitaxel (TC)	2A preferred	No	<a href="#">Phase 3 (GOG 209)</a> , non-inferiority, randomized	Cisplatin + doxorubicin + paclitaxel + filgrastim (TAP)	-----	First-line	<ul style="list-style-type: none"> <li>• TC is not inferior to TAP in terms of PFS and OS. Overall, the toxicity profile favors TC.</li> </ul>
Cisplatin + doxorubicin + paclitaxel (TAP)	2A	No	<a href="#">Phase 3 (GOG 177)</a>	Cisplatin + doxorubicin (AP)	OS	Chemo-therapy naive	<ul style="list-style-type: none"> <li>• TAP significantly improves ORR, PFS, and OS compared with AP</li> </ul>
Bevacizumab	2A (after progression on prior cytotoxic chemo)	No	<a href="#">Phase 2</a>	N/A	6-mon PFS 6-mon OS	Second- or third-line therapy	<ul style="list-style-type: none"> <li>• Bevacizumab is clinically active based on PFS at 6 months of 40.4% in recurrent or persistent endometrial carcinoma</li> </ul>
Paclitaxel	2A	No	<a href="#">GOG study</a>	N/A	-----	Second-line	<ul style="list-style-type: none"> <li>• Paclitaxel is an active agent in the treatment of endometrial cancer in patients who have had prior chemotherapy with an ORR of 27.3%</li> </ul>
Liposomal doxorubicin	2A	No	<a href="#">Phase 2</a>	N/A	-----	Second-line	<ul style="list-style-type: none"> <li>• Liposomal doxorubicin has only limited activity (ORR 9.5%) in pretreated advanced, recurrent endometrial cancer</li> </ul>
Temsirolimus	2A	No	<a href="#">Phase 2</a>	N/A	ORR	All lines of therapy	<ul style="list-style-type: none"> <li>• Temsirolimus demonstrated clinical activity with ORR higher in chemo-naïve patients than in chemo-treated patients</li> </ul>

### 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 maintenance bevacizumab	1 (for unresectable disease only)	No	<a href="#">Phase 3 (MAPS)</a> , multi-center, randomized, controlled, open-label	Cisplatin + pemetrexed	OS	Chemo-naïve	<ul style="list-style-type: none"> <li>• Addition of bevacizumab to pemetrexed plus cisplatin significantly improved OS in malignant pleural mesothelioma at the cost of expected manageable toxic effects, therefore it should be considered as a suitable treatment for the disease.</li> </ul>
Cisplatin + pemetrexed	1	Yes	<a href="#">Phase 3</a> , 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	<a href="#">Phase 2</a>	N/A	PFS	First-line	<ul style="list-style-type: none"> <li>• Bevacizumab, carboplatin, and pemetrexed achieved a 34.2% partial response and 57.9% stable disease.</li> <li>• The primary end point of the trial was not reached</li> </ul>
Carboplatin + pemetrexed	2A	No	<a href="#">Phase 2</a>	N/A	-----	First-line	<ul style="list-style-type: none"> <li>• This combination of carboplatin and pemetrexed is moderately active with an ORR of 25%</li> </ul>
Carboplatin + pemetrexed	2A	No	<a href="#">Phase 2</a> , multi-center	N/A	ORR	Chemo-naïve	<ul style="list-style-type: none"> <li>• Disease control rate, time to disease progression, and overall survival were similar to the results achieved with the standard regimen of pemetrexed and</li> </ul>

							cisplatin, suggesting that the carboplatin combination could be an alternative option for these patients.
Carboplatin + pemetrexed	2A	No					

### AIDS-Related Kaposi Sarcoma

Relapsed/refractory advanced, cutaneous, oral, visceral, or nodal disease							
Regimen	NCCN Category	FDA Approved	Trial Design	Comparator	Primary End-Point	Line of Therapy	Conclusion
Bevacizumab + antiretroviral therapy (ART)	2A (for disease that has progressed on or not responded to first-line systemic therapy, and progressed on alternate first-line systemic therapy)	No	<a href="#">Phase 2</a>	N/A	ORR	Progression after anti-retroviral therapy	<ul style="list-style-type: none"> <li>• Bevacizumab has clinical activity with an ORR of 31%</li> </ul>
Nab-paclitaxel	2A	No	<a href="#">Phase 2</a>	N/A	-----	-----	<ul style="list-style-type: none"> <li>• Nab-paclitaxel demonstrated efficacy in all patients</li> </ul>

Pomalidomide	2A preferred (third-line)	No	<a href="#">Phase 1/2</a>	N/A	ORR	All lines of therapy	<ul style="list-style-type: none"> <li>• Pomalidomide demonstrated an ORR of 73% and is active regardless of HIV status.</li> </ul>
Liposomal doxorubicin	2A	Yes	<a href="#">Phase 2</a>	N/A	-----	After doxorubicin + bleomycin + vincristine (ABV) or bleomycin + vincristine (BV) chemotherapy	<ul style="list-style-type: none"> <li>• Liposomal doxorubicin is effective in treating patients who have experienced failure of standard chemotherapy for AIDS-KS</li> </ul>
Paclitaxel	2A	Yes	<a href="#">Phase 2</a>	N/A	-----	Second-line after anthracycline	<ul style="list-style-type: none"> <li>• Paclitaxel demonstrated an ORR of 71% with responses that correlate to a fall in plasma IL-6 levels</li> </ul>
Etoposide	2A	No	<a href="#">Phase 2</a>	N/A	-----	Subsequent therapy after prior combination chemo or anthracycline therapy	<ul style="list-style-type: none"> <li>• Etoposide has an ORR of 36.1%</li> </ul>
Gemcitabine	2A	No	<a href="#">Phase IIA, randomized</a>	Bleomycin + vincristine (BV)	-----	Subsequent therapy after anti-retroviral therapy	<ul style="list-style-type: none"> <li>• Gemcitabine demonstrated clinical activity with a CR rate of 33.3% in chemotherapy-naïve patients</li> </ul>
Imatinib	2A	No	<a href="#">Phase 2</a>	N/A	ORR	Subsequent therapy after chemo or anti-retroviral therapy	<ul style="list-style-type: none"> <li>• Imatinib has clinical activity in AIDS-KS with a PR of 33.3%</li> </ul>
Interferon alpha-2b (1 million units per day) + zidovudine	2A	No	<a href="#">Prospective randomized trial</a>	Interferon alpha-2b (8 million units per day) + zidovudine	-----	-----	<ul style="list-style-type: none"> <li>• Zidovudine + interferon alpha demonstrated clinical activity with dose-related responses and toxicity</li> </ul>

Thalidomide	2A	No	<a href="#">Phase 2</a> dose-escalation study	N/A	ORR Safety	-----	<ul style="list-style-type: none"> <li>• Thalidomide was found to induce an ORR of 40%.</li> </ul>
Vinorelbine	2A	No	<a href="#">Phase 2</a>	N/A	-----	Second-line or later	<ul style="list-style-type: none"> <li>• Vinorelbine is safe and effective in the treatment of patients with advanced KS who have been previously treated with one or more chemotherapy regimens (ORR 43%).</li> </ul>

### 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 <i>Cervical cancer data</i>	2A preferred	No	<a href="#">Phase 3 (GOG-0240)</a> , randomized, controlled, open-label	Cisplatin + paclitaxel vs. topotecan + cisplatin + paclitaxel vs. topotecan + paclitaxel	OS	Persistent, recurrent, or metastatic <i>cervical cancer</i> (74% had received prior chemoradiation)	<ul style="list-style-type: none"> <li>• Bevacizumab improved survival in patients with advanced <i>cervical cancer</i> with by 3.5 months compared to chemotherapy alone.</li> </ul>
Cisplatin	2A preferred	No	No data				
Carboplatin	2A preferred	No	No data				
Cisplatin + paclitaxel (TP) <i>Cervical cancer data</i>	2A preferred	No	<a href="#">Phase 3 (JCOG0505)</a> , randomized	Carboplatin + paclitaxel (TC)	OS	≤ 1 platinum-regimen and no prior taxane	TC was non-inferior to TP in patients with metastatic or recurrent <i>cervical cancer</i>

Carboplatin + paclitaxel	2A preferred	No	See cisplatin + paclitaxel above
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### 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	<a href="#">Retrospective study</a>	N/A	-----	First- and second-line	<ul style="list-style-type: none"> <li>• Bevacizumab plus chemotherapy demonstrated an OS of 21.9 months.</li> </ul>
Bevacizumab + CapeOx	2A (if appropriate for intensive therapy)	No	<a href="#">Phase 2</a> , single-center, open-label	N/A	6-mon PFS	Untreated disease	<ul style="list-style-type: none"> <li>• The results of the current study indicate that CapeOX with bevacizumab is an active regimen (6-mon PFS rate 68%) for patients with SBA.</li> </ul>
FOLFOX	2A	No	<a href="#">Phase 2</a>	N/A	-----	First-line	<ul style="list-style-type: none"> <li>• The modified FOLFOX as first-line therapy demonstrated an ORR of 48.5% in patients with advanced SBA.</li> </ul>
FOLFOX	2A	No	<a href="#">Phase 2</a> , multi-center, single-arm, open-label	N/A	1-year PFs	First-line	<ul style="list-style-type: none"> <li>• 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.</li> </ul>
CapeOX	2A	No	<a href="#">Phase 2</a>	N/A	ORR	First-line	<ul style="list-style-type: none"> <li>• CapeOX produced an ORR of 50%, with 10% achieving complete response.</li> </ul>