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# INTRAVENOUS ANTI-VEGF AGENTS FOR APPROVED ONCOLOGIC DISORDERS

## BEVACIZUMAB & BIOSIMILARS
## RAMUCIRUMAB
## ZIV-AFLIBERCEPT

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# ABBREVIATIONS

| | |
|---|---|
| 5-FU | 5-flurouracil |
| AFP | alfa fetoprotein |
| AGA | American Gastroenterological Association |
| ASCO | American Society of Clinical Oncology |
| CAPEOX | oxaliplatin + capecitabine |
| ccRCC | clear cell renal cell carcinoma |
| CRC | colorectal cancer |
| dMMR | deficient mismatch repair |
| EGFR | epidermal growth factor receptor |
| FOLFIRI | leucovorin + fluorouracil + irinotecan |
| FOLIRINOX | leucovorin + fluorouracil + irinotecan + oxaliplatin |
| FOLFOX | leucovorin + fluorouracil + oxaliplatin |
| FDA | US Food and Drug Administration |
| GEJ | gastroesophageal junction |
| ICI | immune checkpoint inhibitor |
| IDH | isocitrate dehydrogenase |
| IFL | irinotecan, fluorouracil, and leucovorin |
| IROX | oxaliplatin + irinotecan |
| HBV | hepatitis B virus |
| HCC | hepatocellular cancer |
| HCV | hepatitis C virus |
| H-H | head-to-head |
| HIV | human immunodeficiency virus |
| HRD | homologous recombination deficiency |
| ICIs | immune checkpoint inhibitors |
| IV | intravenous |
| mCRC | metastatic colorectal cancer |
| MMR | mismatch repair |
| mRCC | metastatic renal cell carcinoma |
| MSI | microsatellite instability |
| MSS | microsatellite stable |
| NAFLD | non-alcoholic fatty liver disease |
| NASH | nonalcoholic steatohepatitis |
| NCCN | National Comprehensive Cancer Network |
| nccRCC | non-clear cell renal cell carcinoma |
| NSCLC | non-small cell lung cancer |
| PD-1 | programmed cell death-1 |
| PD-L1 | programmed cell death 1 ligand |

| | |
|---|---|
| PDL | preferred drug list |
| pMMR | proficient mismatch repair |
| PRES | posterior reversible encephalopathy syndrome |
| PS | performance status |
| RCC | renal cell carcinoma |
| RCTs | randomized controlled trials |
| SRs | systematic reviews |
| TKI | tyrosine kinase inhibitor |
| VEGF | vascular endothelial growth factor |
| WHO | World Health Organization |
| WT | wild type |

# EXECUTIVE SUMMARY

Vascular endothelial growth factor (VEGF) inhibitors (ie, anti-VEGF agents) inhibit either extracellular VEGF receptors on endothelial cells or certain VEGF ligands, ultimately reducing the downstream VEGF-signaling transduction pathway that stimulates angiogenesis and, in turn, progression of certain cancers. Intravenous (IV) anti-VEGF agents available in the US include bevacizumab, 4 biosimilars* of originator bevacizumab, ramucirumab, and ziv-aflibercept.

Altogether, approved indications of IV anti-VEGF therapies span many oncologic disorders including metastatic colorectal cancer (mCRC), gastric/esophageal cancer, non-small cell lung cancer (NSCLC), glioblastoma, metastatic renal cell carcinoma (mRCC), cervical cancer, hepatocellular cancer (HCC), and ovarian, fallopian tube, or primary peritoneal cancer. Bevacizumab has the most approved indications, and its 4 biosimilars have most of the originator's indications, with a couple exceptions (eg, no biosimilar is approved for hepatocellular carcinoma).

There are 3 FDA-indicated disease states in common between 2 or more IV anti-VEGF agents: mCRC, HCC, and NSCLC. However, since approved indications are also specific to use as first- or second-line therapy, prior treatment, co-treatments, or other clinical characteristics (eg, genetic mutations or histology), *indications may not fully overlap*:

- **mCRC:** Bevacizumab/biosimilars are approved for mCRC *first-line or second-line* systemic therapy, whereas ramucirumab is approved for *subsequent* therapy in patients who previously failed a regimen of bevacizumab/oxaliplatin/a fluoropyrimidine.[1-6] Ziv-aflibercept is also approved for *subsequent* therapy after failure of an oxaliplatin-containing regimen.[7]
- **HCC**: Bevacizumab (originator only; in combination with atezolizumab) is approved for advanced HCC (unresectable or metastatic) in patients naive to prior systemic therapy; whereas, ramucirumab is approved for *subsequent* therapy of advanced HCC in patients with prior failure on sorafenib and who also have alpha fetoprotein levels ≥400 ng/mL.[2,3]
- **NSCLC**: While bevacizumab (in combination with carboplatin/paclitaxel) and ramucirumab (in combination with erlotinib) are approved for *first-line* systemic therapy of advanced NSCLC, bevacizumab is indicated only for *non-squamous* NSCLC histology, and ramucirumab is indicated first-line only in the presence of certain mutations (EGFR exon 19 deletion or exon 21 substitution).[1-6] Additionally, ramucirumab (in combination with docetaxel) is indicated for *subsequent* therapy of NSCLC in general, after progression on platinum-based chemotherapy.[3]

Individually, bevacizumab/biosimilars and ramucirumab, have unique indicated disease states that other IV anti-VEGF agents do not have. Bevacizumab/biosimilars are uniquely indicated for cervical cancer, glioblastoma, renal cell carcinoma, and epithelial ovarian, fallopian tube, or peritoneal cancer.[1,2,4-6] Ramucirumab is uniquely indicated for gastric/esophageal cancers.[3] Product labeling (ie, package inserts) for the reviewed IV anti-VEGF agents describe that the safety and effectiveness have not been established in the pediatric population.

* Biosimilars of originator Avastin (bevacizumab) include Alymsys (bevacizumab-maly), Mvasi (bevacizumab-awwb), Vegzelma (bevacizumab-adcd), and Zirabev (bevacizumab-bvzr)

Guidelines by the National Comprehensive Cancer Network (NCCN) for oncologic disorders are up to date and are often updated on a yearly basis. A common theme among reviewed NCCN guidelines is that wherever bevacizumab is specified as a treatment option, authors also consider an FDA-biosimilar an acceptable substitute for the originator (including in the setting of HCC). For mCRC, when the 3 IV anti-VEGF agents are recommended for the same clinical scenario, preference is given to bevacizumab over ramucirumab or ziv-aflibercept, on the basis of toxicity profiles and/or cost.[8] Moreover, for HCC, bevacizumab-based therapy is a preferred first-line regimen, whereas ramucirumab is reserved for subsequent-line therapy.[9] In NSCLC, bevacizumab and ramucirumab have both overlapping and unique places-in-therapy, without a preference stated by guideline authors in areas of overlap.[10] The place-in-therapy for the IV anti-VEGF agents, according to NCCN guideline recommendations, are summarized in the following bullets with respect to overlapping indication areas:

- In the setting of mCRC, bevacizumab is a recommended treatment option (in combination with other chemotherapies) for either first-line or subsequent-line therapy; whereas, ramucirumab and ziv-aflibercept are recommended primarily in subsequent-line regimens and have a more limited set of clinical scenarios for which they are recommended compared to that of bevacizumab.[8]
- For advanced HCC, the combination of bevacizumab/atezolizumab is a preferred first-line regimen, whereas ramucirumab is among recommended subsequent-line regimens.[9]
- Aligned with the approved indication, bevacizumab is recommended only for *non-squamous* NSCLC, whereas ramucirumab may be used in certain patients with either non-squamous or squamous NSCLC histology. Bevacizumab or ramucirumab, both in combination with erlotinib, are recommended first-line options (but secondary to osimertinib monotherapy) for advanced or metastatic NSCLC that is EGFR mutation positive (exon 19 deletion or exon 21 L858R mutations); the combination with erlotinib is off-label for bevacizumab and on-label for ramucirumab. Additionally, there are many bevacizumab-based regimens recommended as first-line therapy in the setting of non-squamous NSCLC without actionable-driver mutations[†]. Although *first-line* therapy for NSCLC without an actionable-driver mutation is not a recommended clinical scenario for ramucirumab, ramucirumab is recommended broadly for *subsequent-line* therapy.[10]

Of the IV anti-VEGF agents, only bevacizumab has an approved indication for the following disease states and is the only IV anti-VEGF with a recommended place-in-therapy in the NCCN guidelines for these cancers: mRCC, high-grade gliomas, metastatic cervical cancer, and epithelial ovarian, fallopian tube, or primary peritoneal cancer.

- Bevacizumab is recommended as a subsequent-line option for clear cell mRCC, and may be useful for advanced papillary, non-clear cell RCC.[11]
- Systemic therapy with bevacizumab is among preferred options (secondary to enrolling in a clinical trial) for the management of recurrent or progressive high-grade gliomas.[12]
- Bevacizumab is recommended as part of several preferred and alternative regimens for first-line systemic therapy of cervical cancer including squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma; or as monotherapy in second-line or subsequent therapy for recurrent or metastatic disease.[13]

[†] Actionable-driver mutations or alterations refer to certain genetic mutations or molecular features that are unique to the patient's cancer and are predictive of a positive response to a certain therapy. Such mutations or features "drive" the choice of therapy to a particular pharmaceutical designed to target that type of cancer.

- Bevacizumab is recommended in the setting of epithelial ovarian, fallopian tube, or primary peritoneal cancer; it is among preferred and alternative regimens for primary therapy of stage II-IV disease and for recurrent disease.[14]

Regarding other approved indications for ramucirumab, ramucirumab is the only IV anti-VEGF therapy recommended by the NCCN for unresectable, locally advanced, recurrent, or metastatic gastric, esophageal, or gastro-esophageal junction (GEJ) adenocarcinoma, in second-line or subsequent-regimen options.

Following our literature search for direct, head-to-head randomized controlled trials (RCTs), with respect to FDA-indicated disease states in common between the IV anti-VEGF therapies, no RCTs were found that compared bevacizumab, ramucirumab, or ziv-aflibercept. Many recently published systematic reviews (SRs) were open to include comparative studies of interest but corroborate that none are available. The trend is consistent with clinical guidelines which also do not show comparative studies between the IV anti-VEGF agents. This is likely because these agents are either used in differing lines of therapy or were compared to other therapies that were the standard of care at that time.

On the other hand, limited comparative evidence was identified comparing bevacizumab biosimilars to the originator: based on 3 SRs, 1 RCT each is available for 3 biosimilars (Zirabev, Mvasi, and Alymsys) compared to the originator in the setting of non-squamous NSCLC, and 1 RCT compared Alymsys to the originator for the treatment of mCRC. No notable safety or efficacy differences were found between the originator and biosimilars, based on meta-analysis or individual RCT data as reported in the SRs for main outcomes of interest including objective response, progression-free survival, or adverse events.[15-17]

Table 18 of this report summarizes recognized off-label uses from Micromedex and Lexicomp drug-information compendia. Bevacizumab has many off-label uses categorized by Micromedex as “effective” or “evidence favors efficacy”; and several bevacizumab off-label indications are noted by Lexicomp as guideline recommended (for the treatment of age-related macular degeneration, diabetic macular edema, hereditary hemorrhagic telangiectasia, and malignant pleural mesothelioma).[18,19] Among the compendia, only 1 off-label use is listed for ramucirumab or ziv-aflibercept.[18,19]

IV anti-VEGF therapies share many warnings in common. As a class, they impede wound healing and may be associated with elevated risk of hemorrhage, GI perforation, thromboembolic events, hypertension, proteinuria, and a neurologic disorder called posterior reversable encephalopathy syndrome.[1-6] A warning regarding infusion reactions, some potentially severe, is specified for bevacizumab and ramucirumab. Premedication with an antihistamine (with or without a corticosteroid) is recommended prior to ramucirumab administration. Additionally, patients should receive bevacizumab/biosimilars and ramucirumab infusions in a healthcare setting where close monitoring can be employed following administration and where resuscitation equipment is readily available.

In general, common side effects listed for agents depend on the study population and the therapeutic regimen applied. Neutropenia was reported as a common adverse event (and numerically higher than the comparator group) for each IV anti-VEGF agent with respect to particular populations and treatment regimens. Although the IV anti-VEGF agents are not contraindicated in pregnancy, their mechanism of action and animal studies implicate angiogenesis and the VEGF pathway in critical aspects of reproduction, embryo-fetal development, and postnatal development. Animal models have

demonstrated fetal harm with bevacizumab and ziv-aflibercept at clinically relevant therapeutic exposures, while ramucirumab has not been tested in animal embryo-fetal studies.[1-6]

Considering the wider range of indicated oncologic disease groups for bevacizumab (7), compared to ramucirumab (4) and ziv-aflibercept (1), in addition to the many recognized off-label uses of bevacizumab, a bevacizumab-based IV anti-VEGF formulation (ie, originator or FDA-approved biosimilar) may be considered for preference on the Utah Medicaid Preferred Drug List. An FDA-approved biosimilar is considered an acceptable substitute by the NCCN guidelines for originator bevacizumab for reviewed on-label indications covered in this report where bevacizumab is recommended. Non-preferred products may be made available via prior authorization, especially to accommodate clinical scenarios for which bevacizumab is neither approved or guideline recommended, or for scenarios where bevacizumab is recommended secondarily to another IV anti-VEGF therapy.

# 1.0 INTRODUCTION

Intravenous (IV) Vascular Endothelial Growth Factor (VEGF) inhibitors include bevacizumab, 4 biosimilars of the originator bevacizumab, ramucirumab, and ziv-aflibercept (formulations shown in **Table 1**). Collectively, these products are approved for the treatment of many oncologic disorders including colorectal cancer (CRC), gastric/esophageal cancer, non-small cell lung cancer (NSCLC), glioblastoma, renal cell carcinoma, hepatocellular cancer (HCC), cervical cancer, and epithelial ovarian, fallopian tube, or primary peritoneal cancer, as illustrated in **Table 2**.

Of the IV anti-VEGF agents, bevacizumab (as the originator product, Avastin) has the most approved indications.[1-7] Its biosimilars have a majority but not all the originator's indications. Ramucirumab has 1 uniquely indicated oncologic disease group compared to the other IV anti-VEGF agents (for gastric/esophageal cancers). Ziv-aflibercept has only 1 approved indication (for CRC)— the indicated disease overlaps with that of other IV anti-VEGFs. Across the IV anti-VEGF agents, there are 3 US Food and Drug Administration (FDA)-indicated disease states in common: metastatic colorectal cancer, hepatocellular cancer, and non-small cell lung cancer. Nonetheless, since approved indications are also specific to use as first- or second-line therapy, co-treatments, or other clinical characteristics, the indications may not fully overlap.[‡] There is no specified approved age for use for all but 1 indication of these agents (bevacizumab for recurrent glioblastoma in *adults*); nonetheless, the package insert for each agent describes that safety and efficacy have not been established in the pediatric population.[1-7]

This review focuses on approved indications, the place-in-therapy per recent clinical guidelines (particularly those by the National Comprehensive Cancer Network [NCCN]) for approved indications and labeled safety information of the IV anti-VEGF products. Additionally, a literature search for direct, head-to-head comparative randomized controlled trial (RCT) information was conducted with respect to FDA-indicated disease states in common between the IV anti-VEGF therapies, to further inform decision-making regarding the Utah Medicaid Preferred Drug List (PDL). This report serves as a companion to a future planned report that will be prepared for the *oral* anti-VEGF therapies (to be presented in May 2024). Currently, the Utah Medicaid PDL does not include anti-VEGF products of any formulation, but a prior authorization is in place for anti-VEGF therapy.

This report does not review the place in therapy for surgical resection, ablative procedures, embolization approaches, radiation therapy, or transplantation. Chemotherapy is addressed primarily in the context of combination regimens with anti-VEGF agents. The complex processes regarding diagnosis of the indicated cancers are not reviewed. Yet, recommendations regarding pertinent biomarkers of these diseases may be addressed as they relate to pharmacotherapy decision-making.

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[‡] Refer to **Table A1** of Appendix A to view the applicable co-treatments (ie, treatment regimen) specified as part of the approved indication and recommended dose for each of these agents.

**Table 1** shows the intravenous formulations of the reviewed products. The originator of bevacizumab, Avastin, was originally approved in 2004. Its biosimilars were approved from 2017 onward. Ziv-aflibercept was approved in 2012 and ramucirumab in 2014.

*Table 1. Anti-VEGF Intravenous Solution Formulations*[1-7]

| Active Ingredient | Formulations |
|---|---|
| Bevacizumab & Biosimilars | **Vegzelma*** (bevacizumab-adcd) 25 mg/mL; 4 mL and 16 mL single dose vials<br>*Preservative Free*<br>**Alymsys*** (bevacizumab-maly) 25 mg/mL; 4 mL and 16 mL single dose vials<br>**Avastin** (bevacizumab) 25 mg/mL; 4 mL and 16 mL single dose vials<br>**Mvasi*** (bevacizumab-awwb) 25 mg/mL; 4 mL and 16 mL single dose vials<br>**Zirabev*** (bevacizumab-bvzr) 25 mg/mL; 4 mL and 16 mL single dose vials |
| Ramucirumab | *Preservative Free*<br>**Cyramza** (ramucirumab) 10 mg/mL; 10 mL and 50 mL single dose vials |
| Ziv-aflibercept | *Preservative Free*<br>**Zaltrap** (ziv-aflibercept) 25 mg/mL; 4 mL and 8 mL single-dose vials |

**Denotes biosimilars of the originator, Avastin (bevacizumab)*

*Note: All vials mentioned in the table require storage under refrigeration prior to preparation for administration. Once prepared (diluted) accordingly, the Vegzelma formulation of bevacizumab with preservative can be stored longer under refrigeration (up to 24 hours) or at room temperature (up to 4 hours) if not used immediately, compared to the bevacizumab formulations without preservatives which can only be stored under refrigeration up to 4-8 hours, depending on the product.*

*Table 2. IV Anti-VEGF Products by Indicated Disease State*[1-7,a]

| Products | Cervical cancer | Colorectal cancer, metastatic | Gastric or esophagogastric cancer, advanced or metastatic | Glio-blastoma, recurrent | Hepatocellular carcinoma, advanced | Non-small cell lung cancer (NSCLC), advanced | Epithelial ovarian, fallopian tube or primary peritoneal cancer | Renal cell carcinoma, metastatic |
|---|---|---|---|---|---|---|---|---|
| **Bevacizumab** (Avastin) | X | X | | X | X (first-line therapy) | X (for non-squamous histology only) | X[b] | X |
| ***Bevacizumab Biosimilars*** **Mvasi** (bevacizumab-awwb) **Vegzelma** (bevacizumab-adcd) **Zirabev** (bevacizumab-bvzr) **Alymsys** (bevacizumab-maly) | | | | | *Biosimilars do not have this approved indication* | | | |
| **Ramucirumab** (Cyramza) | | X (for progression after bevacizumab) | X (for progression after a fluoropyrimidine or platinum regimen) | | X (for cases with prior sorafenib treatment and AFP≥400) | X (first-line for cases with certain EGFR mutations; or for progression after a platinum regimen) | | |
| **Ziv-aflibercept** (Zaltrap) | | X (for progression/ resistance after an oxaliplatin regimen) | | | | | | |

*Abbreviations: AFP, alpha fetoprotein; EGFR, epidermal growth factor receptor; IV, intravenous*

*[a] Table A1 of Appendix A includes all labeled indications and dosing for these agents*

*[b] Refer to Table 3 to see the subgroup of patients with the specified cancer who are indicated for this product; Alymsys does not have the full span of indicated patients for the respective cancer compared to the originator and other biosimilars of bevacizumab*

# 2.0 METHODS

The following websites were screened for treatment guidelines for cancers applicable to the FDA-approved uses of IV anti-VEGF therapies:

I. The National Comprehensive Cancer Network (**NCCN**): https://www.nccn.org/guidelines/category_1
II. American Society of Clinical Oncology (**ASCO**): www.asco.org/practice-patients/guidelines
III. American Gastroenterological Association (**AGA**): https://gastro.org/clinical-guidance/
IV. American College of Chest Physicians: www.org/Guidelines/Thoracic-Oncology
V. Lexicomp *Clinical Practice Guidelines* link among drug monographs

The NCCN guidelines were the focus of the review for the guideline information sections of this report; these were often the most updated US guidelines for the reviewed indications. Nonetheless, information from ASCO and/or other relatively recent guidelines were also incorporated, particularly for indications where more than 1 IV anti-VEGF therapy is approved (ie, metastatic colorectal cancer, advanced hepatocellular carcinoma, and advanced non-small cell lung cancer indications).

For product prescribing information (ie, product labeling, package inserts), we searched the drug sponsor's website for each brand product if available, otherwise, Drugs@FDA and dailymed.nlm.nih.gov.

***Literature Search for Comparative Evidence with Respect to Overlapping Approved Indications***

Targeted search strategies were developed in a phased approach to identify systematic reviews (SRs) of randomized controlled trials (RCTs) for the reviewed agents respective to their FDA-approved indications in common. Overlapping indicated disease states among the reviewed IV anti-VEGF products include colorectal cancer, hepatocellular carcinoma, and non-small cell lung cancer. The phased approach incorporated searching and screening of most recently published SRs first, then refining the search to later publication years tailored to certain drugs/indications as needed (per the rationale described in Table B1 of Appendix B).

Recent SRs (eg, published over the last 3 years) were searched for in Ovid-Medline and in Epistemonikos, a medical literature database consolidating SRs from Cochrane, Pubmed, Embase, CINAHL, and others. Supplemental searches for individual RCTs were conducted in Ovid-Medline and Embase. Strategies in Ovid-Medline consisted of controlled vocabulary (ie, Medical Subject Headings [MeSH]) and keyword phrases for active ingredients and overlapping approved indications. Strategies in Epistemonikos consisted of keyword phrases with Boolean operators. A combination of independently derived filters was used to identify SRs in Ovid-Medline. Search filters for RCTs were applied using options referred to in the Cochrane Collaboration Handbook for SRs (Ovid-Medline[20] and Embase[21]). See **Appendix B** for search strategy details.

*Screening*: The lead author independently screened all search result records (titles/abstracts/full texts) for inclusion. **Appendix C** shows the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow chart for the literature screening process.

*Inclusion and Exclusion Criteria for Comparative Evidence*: Eligible reports were either SRs with RCTs of head-to-head parallel study arms, or individual RCTs, directly comparing 2 IV anti-VEGF products listed in

Table 1 with respect to overlapping approved diseases/indications. Direct pair-wise meta-analysis data or result data from individual RCTs with direct comparisons were eligible for inclusion. Refer to section 8.0 for a summary of the included studies, and Appendix D for a list of excluded studies during full-text screening.

## 3.0 MECHANISM OF ACTION

The reviewed IV anti-VEGF agents inhibit either the extracellular VEGF receptors on endothelial cells or certain VEGF ligands, ultimately reducing the downstream VEGF signaling transduction pathway that stimulates angiogenesis (growth of microvasculature). Blockade of VEGF is thought to impact cancer by cutting off nutrient supply to tumor cells; though there may also be other mechanisms by which these agents impede tumor growth (eg, direct effects on tumor cells, or normalization of vessels), effects which may also be unique to the type of cancer.[22]

The endogenous VEGF-A ligand activates VEGF receptors and promotes endothelial cell proliferation, angiogenesis, and vascular permeability.[23,24] Bevacizumab is a monoclonal antibody against VEGF-A.[23] Ramucirumab is an antibody against VEGF-receptor 2, blocking the binding of VEGF ligands (A, C, and D; the latter 2 are involved in lymphangiogenesis[24]).[3] Ziv-aflibercept is comprised of portions of the human extracellular VEGF receptors 1 and 2, fused to the Fc portion of human immunoglobulin-G1. It binds VEGF ligands (A, B, and placental growth factor, which all stimulate angiogenesis) preventing activation of VEGF receptors.[7,8]

## 4.0 APPROVED INDICATIONS OF IV ANTI-VEGF AGENTS

**Table 3** shows the clinical scenarios for which IV anti-VEGF agents are indicated (including indication specifications regarding prior treatment, other clinical characteristics, and co-treatments as applicable).

Of the IV anti-VEGF agents, bevacizumab (as the originator product, Avastin) has the most approved indications. Its biosimilars have most of the originator's indications, with a couple exceptions: none of the biosimilars are approved yet for hepatocellular carcinoma, and Alymsys (bevacizumab-maly) has 1 of 3 approved scenarios for epithelial ovarian, fallopian tube, or peritoneal cancer compared to the originator.[1,4-6] Ramucirumab has 1 completely unique indication from the other IV anti-VEGF agents (for gastric/esophageal cancer) and has 3 related but not fully overlapping indications with bevacizumab. For instance, ramucirumab is approved for (a) metastatic colorectal cancer with disease progression *on prior bevacizumab* treatment, and (b) for second-line treatment of hepatocellular cancer; whereas, bevacizumab is not restricted to second-line treatment in these conditions.[2,3] Though both are approved for NSCLC, ramucirumab and bevacizumab are indicated for partially overlapping sets of patients: bevacizumab is indicated for first-line systemic therapy only for *non-squamous* NSCLC; whereas, ramucirumab can be used regardless of squamous histology, but its indication for first-line therapy of NSCLC requires the presence of certain genomic mutations (EGFR exon 19 or exon 21 mutation) that are not required for the bevacizumab indication.[2,3] Ziv-aflibercept has only 1 approved indication that is related to that of bevacizumab but not fully overlapping (for metastatic colorectal cancer [mCRC] second-line therapy only[7]). Overall, FDA-approved indications for anti-VEGF products may be specific to clinical characteristics of the cancer, pre-treatment status, and may specify particular co-treatments.

*Table 3. IV Anti-VEGF Indications*[1-7]

| Indicated Agent | Indicated Clinical Scenario |
|---|---|
| ***Cervical cancer, persistent, recurrent, or metastatic*** | |
| Bevacizumab/biosimilars | For use in combination with paclitaxel/cisplatin or paclitaxel/topotecan |
| ***Colorectal cancer, metastatic (mCRC)*** | |
| Bevacizumab/biosimilars | For first- or second-line treatment, combined with fluorouracil-based chemotherapy; or for second-line treatment after progression on a first-line bevacizumab regimen, used in combination with fluoropyrimidine/oxaliplatin regimen |
| Ramucirumab | For mCRC disease progression on or after bevacizumab/oxaliplatin/a fluoropyrimidine; used in combination with FOLFIRI |
| Ziv-aflibercept | For mCRC resistance or progression of disease following an oxaliplatin-containing regimen; used in combination with FOLFIRI |
| ***Esophagogastric cancer, advanced or metastatic*** | |
| Ramucirumab | For mCRC disease progression on or after fluoropyrimidine- or platinum-containing chemotherapy; used as monotherapy or with paclitaxel |
| ***Glioblastoma*** | |
| Bevacizumab/biosimilars | For recurrent disease in adults |
| ***Hepatocellular carcinoma (HCC)*** | |
| Bevacizumab, originator only | For unresectable or metastatic disease in patients who have not had prior systemic therapy; used in combination with atezolizumab |
| Ramucirumab | For disease post sorafenib-treatment, with alpha fetoprotein of ≥400 ng/mL |
| ***Non-small cell lung cancer (NSCLC)*** | |
| Bevacizumab/biosimilars | For first-line treatment of unresectable, locally advanced, recurrent or metastatic non-squamous NSCLC, used in combination with carboplatin/paclitaxel |
| Ramucirumab | For metastatic disease (a) first-line treatment for tumors with EGFR exon 19 or exon 21 (L858R) mutation, in combination with erlotinib; or (b) for disease progression on or after platinum-based chemotherapy, in combination with docetaxel |
| ***Ovarian (epithelial), fallopian tube or primary peritoneal cancer*** | |
| Bevacizumab/biosimilars | For platinum-resistant recurrent disease treated with no more than 2 prior chemotherapy regimens; used in combination with paclitaxel/pegylated liposomal doxorubicin or topotecan |
| Bevacizumab/ biosimilars except for Alymsys | For stage III or IV disease following initial surgical resection; used in combination with carboplatin/paclitaxel |
| | For platinum-sensitive recurrent disease; used following carboplatin/paclitaxel or carboplatin/gemcitabine |
| ***Renal cell carcinoma, metastatic*** | |
| Bevacizumab/all biosimilars | For use in combination with interferon alpha |

*Abbreviations: EGFR, epidermal growth factor receptor; FOLFIRI, fluorouracil, leucovorin, irinotecan; mCRC, metastatic colorectal cancer; NSCLC, non-small cell lung cancer*

Dosing for bevacizumab is 5-10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks, depending on the indication, infused over 60 to 90 minutes[§]. Ramucirumab dosing is 8-10 mg/kg every 2-3 weeks depending on the indication, infused over 30 to 60 minutes. Prior to each ramucirumab infusion, patients should be premedicated with an IV histamine-1 receptor antagonist (H1RA) due to the risk of hypersensitivity. Patients with a prior infusion reaction to ramucirumab of grade 1 or 2 should be premedicated with an IV H1RA, dexamethasone (or equivalent), and acetaminophen, and the infusion rate should be reduced by 50%. Ramucirumab is not recommended following a grade 3 infusion reaction. Ziv-aflibercept dosing is 4 mg/kg every 2 weeks, infused over 1 hour.[1-7] Refer to Table A1 of Appendix A to view the dosages per approved indication.

# 5.0 SPECIAL POPULATIONS

Although anti-VEGF agents are not expressly contraindicated during **pregnancy**, their mechanism of action and findings from animal studies implicate angiogenesis, as well as VEGF ligand and VEGF receptor 2 in critical aspects of reproduction, embryo-fetal development, and postnatal development. Animal models have demonstrated fetal harm (congenital malformations) with bevacizumab used at the clinical dose (10 mg/kg), as well as embryotoxic/teratogenic effects with ziv-aflibercept at low exposure levels (4 mg/kg).[2,7] Ramucirumab has not been studied in animal embryo-fetal studies.[3] Pregnant women should be advised of the potential risk to a fetus.

Product labeling (ie, package inserts) for the reviewed agents describe that their safety and efficacy have not been established in the **pediatric population**.[1-7]

Refer to **Table 4** for **renal and hepatic impairment** information for the reviewed agents.

*Table 4. Renal and Hepatic Impairment Information[1-7]*

| | |
|---|---|
| **Renal dose adjustment** | No adjustment is specified for any of the reviewed agents: bevacizumab/biosimilars, ramucirumab, and ziv-aflibercept |
| **Hepatic dose adjustment** | Ziv-aflibercept: has not been studied in severe impairment; no adjustment is provided for mild or moderate impairment<br>Bevacizumab/biosimilars: No adjustment is provided<br>Ramucirumab: package insert notes that clinical deterioration occurred in patients with Child-Pugh class B or C cirrhosis without providing a dose adjustment. There are also no adjustments recommended for mild to moderate impairment. |

[§] When administering bevacizumab or ramucirumab, the first dose is given according to the longer infusion duration stated, while the shorter infusion duration may be used at subsequent administrations if the initial infusion duration was tolerated.

# 6.0 DISEASE OVERVIEW & GUIDELINE PLACE IN THERAPY FOR IV ANTI-VEGF AGENTS

The following subsections are organized according to overlapping indicated disease states among IV anti-VEGF agents: metastatic colorectal cancer (Section 6.1), hepatocellular carcinoma (Section 6.2), and non-small cell lung cancer (Section 6.3). Thereafter, subsections address remaining approved indications that are unique to particular agents (applicable to bevacizumab/biosimilars [Section 6.4], and ramucirumab [Section 6.5]).

National Comprehensive Cancer Network (NCCN) guidelines referenced in this report are as follows:

- NCCN Colon Cancer guideline (*Version 4.2023—Nov. 2023*)
- NCCN Hepatocellular Carcinoma guideline (*Version 2.2023—Sep. 2023*)
- NCCN Non-Small Cell Lung Cancer guideline (*Version 1.2024— Dec. 2023*)
- NCCN Central Nervous System Cancers guideline (Version 1.2023— March 2023)
- NCCN Kidney Cancer guideline (*Version 2.2024—Jan. 2024*)
- NCCN Cervical Cancer guideline (*Version 1.2024— Sep. 2023*)
- NCCN Ovarian Cancer, Including Fallopian Tube Cancer, and Primary Peritoneal Cancer guideline (*Version 1.2024— Jan. 2024*)
- NCCN Esophageal and Esophagogastric Junction Cancers guideline (*Version 3.2023*—August 2023)
- NCCN Gastric Cancer guideline (Version 2.2023—August 2023)

The NCCN guidelines categorize recommended regimens either as “preferred”, “other recommended”, or “useful in certain circumstances”; multiple regimen options may be listed in each recommendation category. Descriptions of each category are as follows:

- *Preferred*: interventions are preferrable “…based on superior efficacy, safety, and evidence; and, when appropriate, affordability" (NCCN, page 63).[8]
- *Other recommended*: interventions that are “…somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes,” relative to preferred options (NCCN, page 63).[8]
- *Useful in certain circumstances*: “…may be used for selected patient populations…” (NCCN, page 63).[8]

The following classes of medications, in addition to anti-VEGFs, are referred to in the following subsections when discussing recommended regimens:

- **Antiangiogenic drugs,** a broad pharmacologic class which includes certain **tyrosine kinase inhibitors** (**TKIs**; eg, sorafenib, lenvatinib, regorafenib, and cabozantinib) as well as **anti-VEGF medications**.[25]
- **Endothelial growth factor receptor (EGFR) inhibitors** including certain TKIs (eg, afatinib, erlotinib, gefitinib, osimertinib, dacomitinib, lapatinib) and monoclonal antibodies (eg, cetuximab, panitumumab, amivantamab, necitumumab)
- **Immune check point inhibitors** (ICIs) include programmed cell death-1 (PD-1) receptor and PD-1 ligand (PD-L1) inhibitors (eg, nivolumab, pembrolizumab, durvalumab, dostarlimab, and atezolizumab); and inhibitors of cytotoxic T-lymphocyte-associated protein 4 (CTLA4; eg, tremelimumab and ipilimumab).[25]

## 6.1 Metastatic Colorectal Cancer (mCRC)

In 2020 colorectal cancer (CRC) was attributed to the 4th highest cancer-related incidence in the US (age-adjusted rate: 33 per 100,000 people) and the 4th highest cancer-related death rate (age-adjusted rate: 13 per 100,000 people). However, Utah rates are generally lower than national rates (age-adjusted incidence rate of CRC is 27).[26] Approximately 50-60% of CRC cases progress to metastatic disease, most often spreading to the liver and sometimes to the lungs.[8] The 5-year survival rate of mCRC is 14%.[27] Risk factors for CRC include having a first-degree relative with CRC; having a history of Lynch syndrome or inflammatory bowel disease; and possibly vitamin D deficiency, smoking, red/processed meat consumption, alcohol consumption, diabetes mellitus, metabolic syndrome, and obesity.[8]

Biomarkers guide pharmacotherapy treatment decision-making for colorectal cancer. The NCCN recommends that all patients with mCRC should undergo tumor genotype assessment for RAS and BRAF mutations, as well as assessment for HER2 amplifications and mismatch repair (MMR) status (or microsatellite instability [MSI] or stability [MSS]).[8] The following bullets describe key CRC molecular categories:

- MMR deficiency (dMMR) and MSI refer to an endogenous DNA mismatch repair (MMR) system that insufficiently repairs DNA and can lead to accumulation of mutations[28]
  - MMR or MSI status testing is recommended to characterize all patients with colon cancer[8]
  - 15% of CRC cases are dMMR/MSI[28]
- RAS gene mutations: genetic mutations in exon 2, 3, or 4 of KRAS or NRAS genes
  - Testing for RAS mutations is recommended in all patients with mCRC[8]
  - Patients with RAS-related mutations should not be treated with the anti-EGFR therapies, cetuximab- or panitumumab-containing regimens, unless part of a regimen targeting a KRAS G12C mutation[8]
- BRAF gene mutation: genetic mutation of type V600E
  - Testing for BRAF mutation is recommended in all patients with mCRC[8]
  - An estimated 5-9% of mCRC cases are BRAF positive; generally limited to tumors without RAS mutations
  - Cetuximab and panitumumab must be given with a BRAF inhibitor (encorafenib) in the presence of BRAF mutation[8]
- HER2 positive: overexpression of HER2 protein
  - Testing is reserved to cases without RAS or BRAF mutations (ie, *wild-type* BRAF and *wild-type* RAS)[8]
  - HER2-amplified tumors occur in approximately 3% of CRC cases
  - Anti-HER2 therapy is indicated in HER2-amplified tumors that are RAS/BRAF wild-type (WT; ie, negative for RAS/BRAF CRC-related mutations)[8]
- Other mutational biomarkers exist but occur less frequently (eg, NTRK Fusions [0.35% of CRC cases; may indicate treatment with entrectinib or larotrectinib]; RET Fusions [<1% of cases; may indicate selpercatinib treatment]).[8]

All IV anti-VEGF agents are approved for the treatment of mCRC; however, their indications differ regarding prior treatment failure and/or concurrent therapy. **Table 5** summarizes indications and recommended dosing for these indicated therapies.

*Table 5. Intravenous Anti-VEGF Indications and Dosing for Colorectal Cancer*[1-7]

| | |
|---|---|
| **Bevacizumab and Biosimilars** | **Colorectal cancer (metastatic)**<br>• 5 or 10 mg/kg every 2 weeks combined with IV fluorouracil-based chemotherapy for first- or second-line treatment<br>• 5 mg/ kg every 2 weeks or 7.5 mg/kg every 3 weeks combined with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy for second-line treatment in patients who have progressed on a first-line bevacizumab regimen |
| **Ramucirumab** | **Colorectal cancer (metastatic)** with disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine<br>• 8 mg/kg every 2 weeks prior to fluorouracil, leucovorin, and irinotecan (FOLFIRI) |
| **Ziv-aflibercept** | **Colorectal cancer (metastatic)** that is resistant to or has progressed following an oxaliplatin-containing regimen<br>• 4 mg/kg as an intravenous infusion over 1 hour every 2 weeks, in combination with fluorouracil, leucovorin, irinotecan (FOLFIRI) |

### 6.1.1 Key Recommendations for IV Anti-VEGF Therapies

According to the 2023 NCCN guideline, IV anti-VEGF therapies are generally used in combination with a chemotherapy backbone** for the treatment of mCRC.[8] Bevacizumab-based therapy is recommended for first-line or subsequent-line therapy; whereas, ramucirumab and ziv-aflibercept are recommended primarily in subsequent-line regimens and have a more limited set of mCRC clinical scenarios in which they are recommended compared to bevacizumab. Moreover, when multiple IV anti-VEGF agents are listed as treatment options for subsequent therapy, bevacizumab-based therapy is preferred by NCCN over ziv-aflibercept and ramucirumab, based on toxicity profiles and/or cost. Notably, an FDA-approved biosimilar is considered an acceptable substitute for originator bevacizumab.[8] **Table 6** summarizes NCCN treatment recommendations for IV anti-VEGF agents in CRC.

A regimen with bevacizumab (or biosimilar) is among NCCN recommended options for the following[8]:

- Proficient mismatch repair (pMMR)/microsatellite stable (MSS) unresectable mCRC (with synchronous liver and/or lung metastases only); in combination with FOLFIRI or FOLFOX or CAPEOX or FOLFIRINOX
- pMMR/MSS CRC (advanced or metastatic disease) ineligible for or with progression on checkpoint inhibitor†† immunotherapy as part of an initial regimen, or as part of subsequent therapy in patients

** Abbreviations for certain chemotherapy backbones referred to in this section include: CAPEOX, oxaliplatin + capecitabine; FOLFIRI, leucovorin + fluorouracil + irinotecan; FOLFOX; leucovorin + fluorouracil + oxaliplatin; FOLFIRINOX, leucovorin + fluorouracil + irinotecan + oxaliplatin; and IROX, oxaliplatin + irinotecan.

†† Check point inhibitors for CRC include nivolumab ± ipilimumab, pembrolizumab, or dostarlimab-gxly.

with or without prior treatment with oxaliplatin-based therapy and/or irinotecan-based therapy. See **Table 6** and/or guideline for clinical scenarios and full regimen.

- pMMR/MSS CRC unresectable metachronous metastatic colon cancer previously treated with FOLFOX/CAPEOX within past 12 months; in combination with FOLFIRI or irinotecan

Ramucirumab or ziv-aflibercept (in combination with FOLFIRI or irinotecan) are NCCN recommended options for the following clinical scenarios[8]:

- pMMR/MSS CRC (advanced or metastatic disease) ineligible for or with progression on checkpoint inhibitor immunotherapy and previously treated with oxaliplatin-based therapy or a regimen without irinotecan or oxaliplatin, as part of subsequent treatment regimens
    - Note that bevacizumab can be used for initial and subsequent treatment regimens, whereas ramucirumab and ziv-aflibercept are recommended in subsequent-therapy regimens only for this clinical scenario.
- pMMR/MSS CRC unresectable metachronous metastatic colon cancer previously treated with FOLFOX/CAPEOX within past 12 months

The NCCN 2023 guideline is the most recently published US guideline for the treatment of advanced CRC. The 2022 ASCO guideline is similar to the NCCN guideline regarding bevacizumab as an option for first-line treatment (with chemotherapy) in patients with initially unresectable MSS or pMMR mCRC; and regarding bevacizumab preferability over anti-EGFR-based therapy for the treatment of right-sided tumors and/or with RAS-mutant mCRC. Yet, the ASCO guideline prefers anti-EGFR-based therapy for first-line treatment over bevacizumab-based therapy in patients with left-sided, treatment-naïve, RAS WT mCRC. The ASCO guideline did not include any recommendations regarding ramucirumab or ziv-aflibercept.[29]

*Table 6. NCCN Colorectal Cancer Guideline, IV Anti-VEGF Treatment Recommendations, 2023* [8,a]

Recommended regimens containing bevacizumab, ramucirumab, or ziv-aflibercept, for all specified clinical scenarios below, are rated as category 2A for level of evidence; the alternative regimens are primary rated as category 2A as well; there are no category 1 rated regimens.[b]

- **pMMR/MSS unresectable colon cancer (synchronous liver and/or lung metastases only): bevacizumab or approved biosimilar to be used in a regimen with** FOLFIRI, FOLFOX, CAPEOX, or FOLFIRINOX; alternative regimens are panitumumab- or cetuximab-based regimens with chemotherapy for KRAS/NRAS/BRAF WT and left-sided tumors only
- **pMMR/MSS unresectable metachronous metastases colon cancer** previously treated with FOLFOX/ CAPEOX within past 12 months; FOLFIRI or irinotecan +/- **bevacizumab** (or approved biosimilar); **bevacizumab preferred** over alternative similar regimens with **ziv-aflibercept or ramucirumab** (plus FOLFIRI or irinotecan); preference is based on toxicity profiles and/or cost.
  - Alternative combination regimens, depending on the genetic mutations, may include chemotherapy +/- cetuximab or panitumumab, encorafenib, trastuzumab, pertuzumab, lapatinib, tucatinib, fam-trastuzumab, deruxtecan-nxki, sotorasib, adagrasib
- **pMMR/MSS colon cancer ineligible for or with progression on checkpoint inhibitor immunotherapy**:
  - *Initial treatment*: **bevacizumab or approved biosimilar** to be used in a regimen with FOLFOX or CAPEOX or FOLFIRI or FOLFIRINOX; other alternative regimens are cetuximab- or panitumumab-based with chemotherapy
  - *Subsequent treatment (with prior oxaliplatin-based therapy without irinotecan):* **bevacizumab or approved biosimilar** to be used in a regimen with FOLFIRI or irinotecan; **bevacizumab preferred** over similar regimens with **ziv-aflibercept or ramucirumab** (plus FOLFIRI or irinotecan); other alternative combination regimens may contain irinotecan, cetuximab, panitumumab, encorafenib, pertuzumab, lapatinib, tucatinib, fam-trastuzumab, deruxtecan-nxki, sotorasib, adagrasib, or fruquintinib, depending on the mutational status of the disease
    - Regorafenib monotherapy, or trifluridine/tipiracil with or without **bevacizumab** are treatment options for later-in-line therapy (ie, second- or third-line subsequent therapy).



*Abbreviations: CAPEOX, oxaliplatin + capecitabine; EGFR, endothelial growth factor receptor; FOLFIRI, leucovorin + fluorouracil + irinotecan; FOLFOX; leucovorin + fluorouracil + oxaliplatin; FOLFIRINOX, leucovorin + fluorouracil + irinotecan + oxaliplatin; IROX, oxaliplatin + irinotecan; MSS, microsatellite stability; NCCN, National Comprehensive Cancer Network; pMMR, proficient mismatch repair; WT, wild-type*

*[a] Recommended agents in alternative regimens depend on the presence of certain genetic markers (KRAS/NRAS/BRAF etc.); refer to full guideline for details on all recommended regimens and circumstances. In general, panitumumab or cetuximab are used for KRAS/NRAS/BRAF WT and left-sided tumors only; encorafenib added to an EGFR inhibitor is used for BRAF V600E mutation positive; fam-trastuzumab is used for HER2 amplified tumors that are also RAS/BRAF WT; NTRK inhibitors, larotrectinib and entrectinib, are active against NTRK fusion mutations; and selpercatinib is used for RET gene fusion-positive.*

*[b] Category 1: recommendation is based upon high-level evidence and a uniform NCCN consensus; Category 2A is based upon lower-level evidence, but with uniform NCCN consensus; Category 2B is based upon lower-level evidence, and majority consensus.*

*Note: aside from the IV anti-VEGF therapies, the oral multi-kinase inhibitor (tyrosine kinase inhibitor [TKI]/anti-VEGF, etc), regorafenib, is among recommended subsequent-therapy options, for patients that have failed standard chemotherapy regimens, for pMMR/MSS colon cancer ineligible for or with progression on checkpoint inhibitor immunotherapy*

*Table 6. NCCN Colorectal Cancer Guideline, IV Anti-VEGF Treatment Recommendations, 2023* [8,a]

- *Subsequent treatment (with prior irinotecan-based therapy without oxaliplatin):* **bevacizumab or approved biosimilar** to be used in a regimen with FOLFOX or CAPEOX; other alternative combination regimens may contain cetuximab, panitumumab, encorafenib, trastuzumab, pertuzumab, lapatinib, tucatinib, fam-trastuzumab, deruxtecan-nxki, sotorasib, adagrasib, or fruquintinib, depending on the mutational status of the disease
  - Regorafenib monotherapy or trifluridine/tipiracil with or without **bevacizumab** are treatment options for later-in-line therapy (ie, second- or third-line subsequent therapy).
- *Subsequent treatment (with prior irinotecan and oxaliplatin treatment):* trifluridine + tipiracil with or without **bevacizumab**; other options include combination regimens with cetuximab, panitumumab, encorafenib, regorafenib monotherapy, trastuzumab, pertuzumab, lapatinib, tucatinib, fam-trastuzumab, deruxtecan-nxki, sotorasib, adagrasib, or fruquintinib, depending on the mutational status
- *Subsequent treatment (without prior irinotecan or oxaliplatin treatment):* **bevacizumab or approved biosimilar** to be used in a regimen with FOLFOX, CAPEOX, FOLFIRI, irinotecan, or irinotecan/oxaliplatin, FOLFIRINOX; **bevacizumab preferred** over similar regimens with **ziv-aflibercept or ramucirumab** (plus FOLFIRI or irinotecan); other alternative regimens contain FOLFOX, CAPEOX, FOLFIRI, irinotecan, encorafenib, cetuximab, panitumumab, trastuzumab, pertuzumab, lapatinib, tucatinib, fam-trastuzumab deruxtecan-nxki, sotorasib, adagrasib, or fruquintinib, depending on the mutational status
  - Regorafenib monotherapy, or trifluridine/tipiracil with or without **bevacizumab** are treatment options for later-in-line therapy (ie, second- or third-line subsequent therapy).



*Abbreviations: CAPEOX, oxaliplatin + capecitabine; EGFR, endothelial growth factor receptor; FOLFIRI, leucovorin + fluorouracil + irinotecan; FOLFOX; leucovorin + fluorouracil + oxaliplatin; FOLFIRINOX, leucovorin + fluorouracil + irinotecan + oxaliplatin; IROX, oxaliplatin + irinotecan; MSS, microsatellite stability; NCCN, National Comprehensive Cancer Network; pMMR, proficient mismatch repair; WT, wild-type*

*[a] Recommended agents in alternative regimens depend on the presence of certain genetic markers (KRAS/NRAS/BRAF etc.); refer to full guideline for details on all recommended regimens and circumstances. In general, panitumumab or cetuximab are used for KRAS/NRAS/BRAF WT and left-sided tumors only; encorafenib added to an EGFR inhibitor is used for BRAF V600E mutation positive; fam-trastuzumab is used for HER2 amplified tumors that are also RAS/BRAF WT; NTRK inhibitors, larotrectinib and entrectinib, are active against NTRK fusion mutations; and selpercatinib is used for RET gene fusion-positive.*

*[b] Category 1: recommendation is based upon high-level evidence and a uniform NCCN consensus; Category 2A is based upon lower-level evidence, but with uniform NCCN consensus; Category 2B is based upon lower-level evidence, and majority consensus.*

*Note: aside from the IV anti-VEGF therapies, the oral multi-kinase inhibitor (tyrosine kinase inhibitor [TKI]/anti-VEGF, etc), regorafenib, is among recommended subsequent-therapy options, for patients that have failed standard chemotherapy regimens, for pMMR/MSS colon cancer ineligible for or with progression on checkpoint inhibitor immunotherapy*

### 6.1.2 Comparative RCTs

Consistent with the NCCN and ASCO guidelines, which are absent of head-to-head IV anti-VEGF comparative RCTs, several recent SRs (systematic reviews published in 2023 and 2022) also show an absence of head-to-head studies of between bevacizumab-[30], ramucirumab-,[31,32] or ziv-aflibercept-containing[33] regimens for the treatment of mCRC.[34] Additional SRs published in 2021 show no head-to-head trials for first-line systemic treatment for mCRC[35,36] and/or second-line treatment.[37,38] A couple SRs report comparative information regarding bevacizumab and its biosimilars for the treatment of CRC; refer to section 8.0 for details/results.

## 6.2 Hepatocellular Carcinoma (HCC)

Data from 2020 showed liver cancer was attributed to the 6th highest cancer-related death rate in the US (age-adjusted rate: 6.5 per 100,000 people).[26] This includes hepatocellular cancer (72% of cases) and intrahepatic bile duct cancer (19% of cases). About 41,200 new cases are diagnosed each year in the US, and the incidence is about 3 times higher in men than in women.[26,27] The 5-year relative survival rate for liver cancer is 21%.[27] Common sites of metastasis include the lungs, adrenal glands, peritoneum, and bone.[39]

Hepatocellular carcinoma stems from cirrhosis and chronic liver diseases. Major risk factors for developing this pathology include hepatitis B virus (HBV) and/or hepatitis C virus (HCV) infection, human immunodeficiency virus (HIV) infection, chronic alcohol consumption, diabetes or obesity-related non-alcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), and genetic hemochromatosis.[39,40] Thus, HCC is often complicated by related co-morbidities.[39] Approximately two-thirds of cases are diagnosed in an advanced disease stage (with high tumor burden or liver decompensation), eliminating the option for potentially curative treatments such as surgical resection, liver transplant, or radiofrequency ablation.[41-43] Advanced HCC is treated with systemic treatment which can typically extend the median survival in symptomatic patients from a matter of months to 1-1.5 years.[43]

Two IV anti-VEGF agents, bevacizumab and ramucirumab, are approved for the treatment of advanced hepatocellular carcinoma; however, their indications differ regarding prior treatment failure, alpha fetoprotein status, and/or concurrent therapy. **Table 7** summarizes indications and recommended dosing for these therapies.

*Table 7. Intravenous Anti-VEGF Indications and Dosing for Advanced Hepatocellular Cancer[2,3]*

| | |
|---|---|
| **Bevacizumab** (originator only) | **Hepatocellular carcinoma** in patients with unresectable or metastatic disease who have not received prior systemic therapy<br>• 15 mg/kg after administration of 1,200mg of atezolizumab every 3 weeks |
| **Ramucirumab** | **Hepatocellular carcinoma** in patients with an alpha fetoprotein (AFP) of ≥400 ng/mL who have been treated with sorafenib<br>• 8 mg/kg every 2 weeks |

### 6.2.1 Key Recommendations for IV Anti-VEGF Therapies

Anti-VEGF systemic therapy is used for the treatment of advanced liver cancer (ie, metastasis, extensive tumor burden, unresectable disease, inadequate hepatic reserve, and/or not candidate for transplant or locoregional therapies[‡‡]).[9] Bevacizumab is an established first-line treatment when used in combination with the immune checkpoint inhibitor, atezolizumab.[44] In a pivotal phase 3 RCT, bevacizumab/atezolizumab outperformed the long-established first-line agent, sorafenib (an oral multi-kinase inhibitor at VEGF receptors, RAF [a tumor promoting kinase], and PDGRF [a growth signaling kinase]).[9,39,45] Thus, bevacizumab/atezolizumab is an NCCN-preferred first-line regimen for patients with Child-Pugh Class A liver function, and may be useful for Child-Pugh Cass B liver function (**Table 8**). An FDA-approved biosimilar is considered an acceptable substitute for originator bevacizumab by the NCCN. Other NCCN-recommended first-line regimens for certain patients with advanced HCC include tremelimumab-actl/durvalumab (also a preferred regimen), sorafenib, lenvatinib, durvalumab, and pembrolizumab.[9]

Compared to placebo, in a phase 3 study of patients previously treated with sorafenib for advanced HCC, ramucirumab improved progression free survival and time to progression, but overall survival was improved only in the subgroup of patients with baseline AFP ≥400 ng/mL and not in the overall included population.[46] Thus, ramucirumab is an NCCN-recommended option for *subsequent therapy* but only for patients with AFP≥ 400 ng/mL and Child-Pugh Class A liver function.[39] Other subsequent-therapy options include regorafenib, cabozantinib, lenvatinib, sorafenib, nivolumab/ipilimumab, pembrolizumab, nivolumab, dostarlimab-gxly, selpercatinib, larotrectinib, and entrectinib.[9]

Of US treatment guidelines, the NCCN guideline for systemic treatment of HCC was most recently published in 2023; older guidelines by the American Gastroenterological Association (AGA; 2022) and the American Society of Clinical Oncology (ASCO; 2020) are also available. Similar to the NCCN guideline, the AGA guideline recommended bevacizumab with atezolizumab as a first-line therapy (preferred over sorafenib), and ramucirumab as a second-line therapy after progression of disease with sorafenib (and with AFP>400 ng/ml), in patients with metastatic HCC with preserved liver function not eligible for locoregional therapies or resection.[47] ASCO recommendations are also similar to the NCCN guideline regarding IV anti-VEGF therapy for first- and second-line systemic treatment.[48]

[‡‡] For example: ablation, arterially directed therapy, or radiation therapy.

*Table 8. NCCN Liver Cancer Guideline, IV Anti-VEGF Treatment Recommendations, 2023[a,9]*

| |
|---|
| **First Line Systemic Therapy**<br>• *Preferred*: Atezolizumab/**bevacizumab** (for Child-Pugh Class A disease; category 1); or tremelimumab-actl + durvalumab (category 1)<br>• *Other recommended alternative regimens* contain sorafenib, lenvatinib, durvalumab, or pembrolizumab<br>• *Useful in certain circumstances*: atezolizumab/**bevacizumab** (for Child-Pugh Class B disease, category 2A), nivolumab (for Child-Pugh Class B disease only), nivolumab/ipilimumab (for TMB-H tumors) |
| **Subsequent-Line Systemic Therapy for Disease Progression**<br>• *Preferred* for Child-Pugh Class A: regorafenib, cabozantinib, lenvatinib, sorafenib (or B7 for sorafenib)<br>• *Other recommended* for Child-Pugh Class A disease: nivolumab/ipilimumab, pembrolizumab<br>*Useful in certain circumstances*: **ramucirumab** (if AFP ≥400 ng/mL and Child-Pugh Class A disease, category 1); nivolumab for Child-Pugh Class B disease; dostarlimab for MSI-H/dMMR tumors; selpercatinib for RET gene fusion-positive tumors; nivolumab/ipilimumab for TMB-H tumors |

*Abbreviations: AFP, alpha fetoprotein; dMMR, mismatch repair deficient; MSI-H, high microsatellite instability; NCCN, National Comprehensive Cancer Network; TMB-H, high tumor mutational burden*

*[a] Refer to full guideline for details on all recommended regimens and circumstances.*
*Evidence/Consensus Category 1: recommendation is based upon high-level evidence and a uniform NCCN consensus; Category 2A is based upon lower-level evidence, but with uniform NCCN consensus; Category 2B is based upon lower-level evidence, and majority consensus.*
*Note: aside from the IV anti-VEGF therapies, several oral anti-VEGF therapies are also options, either for (a) first-line systemic therapy (as 'other recommended'; sorafenib or levatinib, both for Child-Pugh Class A disease), or for (b) subsequent-line therapy (as preferred options: regorafenib, cabozantinib, lenvatinib, or sorafenib)*

### 6.2.2 Comparative RCTs

Consistent with treatment guidelines[9], which are absent of direct head-to-head IV anti-VEGF comparative studies, several recent SRs (from 2023 and 2022) also show that there are no head-to-head RCTs of bevacizumab- or ramucirumab-containing regimens for the treatment of advanced HCC. Moreover, we would not expect bevacizumab and ramucirumab to be compared since one is established for first-line systemic treatment and the other is established only for subsequent therapy. SRs addressed the following treatment areas and show no IV anti-VEGF head-to-head studies for HCC:

- first-line[49-54] or second-line[55] systemic treatment for advanced HCC[56]
- novel combination strategies for unresectable hepatocellular carcinoma[57]
- immune checkpoint inhibitor combinations in advanced HCC[42]

## 6.3 Non-small Cell Lung Cancer (NSCLC)

Pulmonary cancer (lung and bronchus) is attributed to the leading cause of cancer-related death in the US (age-adjusted rate: 31.8 per 100,000 people) but accounts for the 3rd highest cancer-diagnosis incidence rate (age-adjusted rate: 47.1 per 100,000 people), following breast and prostate cancer.[10,26] Non-small cell lung cancer (NSCLC) is the primary type of lung cancer, accounting for approximately 81% of lung cancer cases. Small cell lung cancer is the second most prevalent type accounting for 14% of lung cancer cases.[27] Subcategories of NSCLC include adenocarcinoma (comprising about half of NSCLC cases; originating from mucus glands), squamous cell carcinoma (comprising about a third of NSCLC cases; originating in cells lining the airways and typically more aggressive), adenosquamous carcinoma, large cell carcinoma (about 2% of NSCLC cases; lacks features to define clear lineage), and other rarer forms.[27] The relative 5-year survival rate of NSCLC is 26%.[27]

In order to guide therapy decision-making, testing for certain genetic mutations and biomarkers are recommended for advanced or metastatic NSCLC with an adenocarcinoma component, large cell carcinoma, or NSCLC not otherwise specified (NOS).[10] Molecular and biomarker testing should include the following ten markers: EGFR mutation, ALK, KRAS, ROS1, BRAF V600E, NTRK1/2/3 fusions, MET exon 14 skipping mutation, RET, ERBB2 alterations (eg, HER2), and PD-L1 expression. For advanced/metastatic NSCLC with *squamous cell* histologic type, these molecular tests are advised for consideration, rather than having a strong recommended as with the aforementioned histologies.[10] Caveats with molecular testing are long turnaround times for results and that results may be limited by biopsy tissue specimen quality/quantity.[58] Thus, non-biomarker directed therapy may be started prior to receiving molecular testing results.

Bevacizumab, its biosimilars, and ramucirumab are approved for the treatment of advanced NSCLC; however, their indications differ regarding the cancer status (eg, localized or metastatic), genetic mutational status, and prior and/or concurrent therapies; **Table 9** summarizes indications and recommended dosing.

*Table 9. Intravenous Anti-VEGF Indications and Dosing for Advanced Non-small Cell Lung Cancer[1-6]*

| | |
|---|---|
| **Bevacizumab and Biosimilars** | **Non-squamous non-small cell lung cancer** (unresectable, locally advanced, recurrent, or metastatic)<br>• 15 mg/kg every 3 weeks with carboplatin and paclitaxel for first-line treatment |
| **Ramucirumab** | **Non-small cell lung cancer** (metastatic)<br>• For first-line treatment for tumors with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations.<br>  ○ 10 mg/kg every 2 weeks with daily erlotinib<br>• For disease progression on or after platinum-based chemotherapy[e]<br>  ○ 10 mg/kg on Day 1 of a 21-day cycle prior to docetaxel |

### 6.3.1 Key Recommendations for IV Anti-VEGF Therapies

Targeted therapy is recommended foremost for patients with actionable driver mutations[§§].[10] Another general treatment principle in the NCCN guideline is that bevacizumab is to be used only for non-squamous NSCLC histology, whereas ramucirumab may be used in indicated patients with either non-squamous or squamous histology. When bevacizumab is indicated, an FDA-approved biosimilar is considered an acceptable substitute for originator bevacizumab (**Table 10**).[10]

Bevacizumab or ramucirumab are used for cases with EGFR mutations (exon 19 deletion [Ex19del], exon 21 L858R mutation, or exon 20 mutation). In particular, bevacizumab and ramucirumab are NCCN recommended as first-line therapy options, in combination with erlotinib (a TKI with anti-EGFR activity), for advanced or metastatic NSCLC that is EGFR mutation positive (Ex19del or exon 21 L858R mutations); these are classified as other-recommended regimens, secondary to preferred osimertinib monotherapy.[10] For exon 20 mutations, the treatment algorithm is similar to the scenario without actionable driver mutations where bevacizumab, but not ramucirumab, is among other-recommended first-line regimens.

For advanced or metastatic NSCLC without targetable genomic alterations, chemotherapy plus immunotherapy is NCCN recommended.[10] Bevacizumab is an "other recommended" first-line option added to carboplatin/paclitaxel/atezolizumab. Bevacizumab added to chemotherapy (carboplatin/paclitaxel, carboplatin/pemetrexed, or cisplatin/pemetrexed) may also be useful for first-line therapy in patients with contraindications to PD-1 or PD-L1 inhibitors. Ramucirumab/docetaxel is recommended as a subsequent-line option (as "other recommended") for metastatic NSCLC regardless of histology (ie, squamous or non-squamous).[10]

Similar to the NCCN guideline, the 2023 ASCO guidelines include bevacizumab in various preferred first-line and second-line regimens (see bullets below) for stage 4 NSCLC without targetable genomic alterations; or in first-line regimens for stage 4 NSCLC with certain EGFR mutations (L858R, Ex19del, exon 20 mutation). The ASCO also recommends ramucirumab/erlotinib first-line for stage 4 NSCLC with certain EGFR mutations (L858R, Ex19del).[59,60]

- Bevacizumab or ramucirumab, combined with erlotinib, are among first-line regimens for systemic treatment of EGFR L858R mutant or Ex19del, stage 4 NSCLC (secondary to the preferred treatment, osimertinib).[60] Bevacizumab with platinum-doublet chemotherapy can be used first-line for EGFR exon 20 mutant, stage 4 NSCLC. Unlike the NCCN guideline, the ASCO guideline for NSCLC with ERGR mutations does not specify bevacizumab regimens only for non-squamous NSCLC histology.[60]
- *For patients without actionable driver mutations*, bevacizumab in combination with atezolizumab/carboplatin/paclitaxel is among first-line options for stage 4, non-squamous NSCLC with negative, unknown, or high PD-L1 status and performance status (PS) 0-1 (among most effective regimens). Bevacizumab/carboplatin/paclitaxel is among first-line options for stage IV non squamous NSCLC (among most effective regimens), and bevacizumab/paclitaxel is among second-line therapy for non-squamous NSCLC[59]

[§§] ALK rearrangements, EGFR activating mutations (except for exon 20 mutation), ERBB2 mutations, KRAS p.G12C mutations, METex14 skipping, NTRK1/2/3 fusions, RET rearrangements, ROS1 rearrangements

*Table 10. NCCN Non-small Cell Lung Cancer Guideline, IV Anti-VEGF Recommendations, 2023* [10,a,b]

| **A. First-line systemic therapy for EGFR Exon 19 Deletion or Exon 21 L858R mutation** | |
|---|---|
| *Preferred; category 1:*<br>• Osimertinib | *Other recommended regimens:*<br>• Any of the following monotherapies: Erlotinib, afatinib, dacomitinib, or gefitinib (each category 1)<br>• Osimertinib + pemetrexed + (cisplatin or carboplatin) (for nonsquamous; category 1)<br>• Erlotinib + (**bevacizumab** [for non-squamous histology] **or ramucirumab**) (category 2A) |
| **B. First-line systemic therapy for non-squamous NSCLC (ie, adenocarcinoma, large cell, or NSCLC NOS) with PD-L1>50% and PS 0-2** | |
| *Preferred regimens; category 1:*<br>• Pembrolizumab<br>• Atezolizumab<br>• Carboplatin or cisplatin, plus pemetrexed/pembrolizumab<br>• Cemiplimab with or without pemetrexed/(carboplatin or cisplatin) | *Other recommended regimens:*<br>• Carboplatin/paclitaxel/**bevacizumab**/ atezolizumab (category 1)<br>• See guideline for others |
| **C. First-line systemic therapy for non-squamous NSCLC with PD-L1 1-49% or negative, no other targetable mutation, and PS 0-2** | |
| *Preferred; category 1*:<br>• Pembrolizumab/ (carboplatin or cisplatin)/pemetrexed<br>• Cemiplimab/pemetrexed/ (carboplatin or cisplatin) | *Other recommended:*<br>• Carboplatin/paclitaxel/**bevacizumab**/atezolizumab (category 1)<br>• See guideline for others |
| **D. First-line for adenocarcinoma, large cell, NSCLC NOS (regardless of EGFR exon 20 mutation); with PS 0-1** | | |
| *Preferred; category 1*:<br>• Pembrolizumab/ (carboplatin or cisplatin)/ pemetrexed<br>• Cemiplimab/pemetrexed/ (carboplatin or cisplatin) | *Other recommended:*<br>• Carboplatin/paclitaxel/ **bevacizumab**/ atezolizumab (category 1)<br>• See guideline for others | *Useful for scenarios with contraindications to PD-1 or PD-L1 inhibitors:*<br>• **Bevacizumab** / carboplatin/ paclitaxel or pemetrexed<br>• **Bevacizumab** / cisplatin/pemetrexed<br>• Other platinum- or gemcitabine-based regimens |
| **E. Subsequent systemic therapy for advanced or metastatic non-squamous NSCLC with PS 0-2** | |
| *Preferred; category 1 (for patients without previous immunotherapy)*:<br>• Nivolumab<br>• Pembrolizumab<br>• Atezolizumab | *Other recommended; category 2A (with or without prior immunotherapy)*<br>• **Ramucirumab**/docetaxel<br>• Docetaxel<br>• Albumin-bound paclitaxel<br>• Gemcitabine |



*Abbreviations: PD-L1, programmed cell death 1 ligand; PS, performance status; NOS, not otherwise specified*

*[a] A bevacizumab FDA-approved biosimilar may be used as a substitute for bevacizumab in any of the applicable regimens specifying bevacizumab*

*[b] Refer to guideline for first-line treatment algorithms for other actionable-driver mutations (where IV anti-VEGF therapy is not included) (eg, EGFR S768I L861Q, and/or G719X mutations, EGFR exon 20 insertion, KRAS G12C mutation, ALK or ROS1 rearrangement, BRAF V600E)*

*Evidence/Consensus Category 1: recommendation is based upon high-level evidence and a uniform NCCN consensus; Category 2A is based upon lower-level evidence, but with uniform NCCN consensus; Category 2B is based upon lower-level evidence, and majority consensus.*

### 6.3.2 Comparative RCTs

Consistent with the NCCN guideline, which is absent of head-to-head IV anti-VEGF comparative studies, several recent SRs (from 2023 and 2022) also show that there are no head-to-head studies of between bevacizumab- and ramucirumab-containing regimens for the treatment of advanced or metastatic NSCLC. SRs address the following treatment areas:

- first-line immune checkpoint inhibitor regimens for advanced non-small cell lung cancer[61-64]
- first-line therapies in EGFR-mutated advanced non-small-cell lung cancer[65-69]
- advanced non-small cell lung cancer with negative PD-L1 expression[70]
- first-line treatments for NSCLC with high programmed death ligand-1 expression[71]
- immunotherapy/chemotherapy versus bevacizumab/chemotherapy first-line for treatment of driver-gene negative NSCLC[72]

A couple SRs report comparative information regarding bevacizumab and its biosimilars for the treatment of NSCLC; refer to section 8.0 for details/results.

## 6.4 Indications Unique to Bevacizumab and Its Biosimilars: Glioblastoma, Renal Cell Carcinoma, Cervical Cancer, Ovarian/Fallopian Tube/Peritoneal Cancer

Of the IV anti-VEGF therapies, only bevacizumab and its FDA-approved biosimilars are approved for advanced cervical cancer, glioblastoma, metastatic renal cell carcinoma, and ovarian, fallopian tube, or peritoneal cancers. **Table 11** includes the indications and dosing for bevacizumab and biosimilars.

*Table 11. Indications Unique to Bevacizumab and Biosimilars*[1,2,4-6,a]

**Glioblastoma (recurrent) in adults**

- 10 mg/kg every 2 weeks

**Renal cell carcinoma (metastatic)**

- 10 mg/kg every 2 weeks with interferon alfa

**Cervical cancer (persistent, recurrent, or metastatic)**

- 15 mg/kg every 3 weeks with paclitaxel and cisplatin, or paclitaxel and topotecan

**Epithelial ovarian, fallopian tube, or primary peritoneal cancer**

- For platinum-resistant recurrent disease previously treated with up to 2 prior chemotherapy regimens: 10 mg/kg every 2 weeks with weekly paclitaxel, pegylated liposomal doxorubicin, or topotecan; or 15 mg/kg every 3 weeks with topotecan given every 3 weeks
- For stage III or IV disease following initial surgical resection[b]: 15 mg/kg every 3 weeks with carboplatin/paclitaxel for up to 6 cycles, followed by 15 mg/kg every 3 weeks as a single agent, for a total of up to 22 cycles
- For platinum-sensitive recurrent disease[b]: 15 mg/kg every 3 weeks with carboplatin and paclitaxel for 6-8 cycles, followed by 15 mg/kg every 3 weeks as a single agent; or 15 mg/kg every 3 weeks with carboplatin and gemcitabine for 6-10 cycles, followed by 15 mg/kg every 3 weeks as a single agent

[a] *Biosimilars of the originator bevacizumab include Mvasi, Vegzelma, Zirabev, and Alymsys*

[b] *The biosimilar, Alymsys, does not have this indication; whereas, the originator bevacizumab and other biosimilars do.*

### *6.4.1 Glioblastoma*

Glioblastoma is the most common type of malignant primary brain tumor in adults, occurring in about 3 per 100,000 adults.[73] It occurs more frequently in men than in women, and is very aggressive. The 5-year survival rate of glioblastoma is about 6%.[12] Glioblastoma is a subtype of gliomas (tumors originating from glial cells [ie, astrocytes, oligodendrocytes, and ependymal cells] of the central nervous system) along with 2 others (eg, astrocytoma, and oligodendroglioma).[74]

The World Health Organization (WHO) classification of gliomas has changed considerably over the years. Glioma classification is based on histopathologic appearance and molecular features.[74,75] Tumors previously classified as glioblastoma (prior to 2021) are now classified into 2 categories based on isocitrate dehydrogenases (IDH) mutation status: (a) **glioblastoma** IDH wildtype, WHO grade 4, or (b) **astrocytoma** IDH-mutant, WHO grade 4.[75,76] IDH mutation status differentiates slower growing tumors

(ie, with IDH-mutation) from more aggressive tumors (IDH-wildtype). Notably, bevacizumab has been approved for glioblastoma since 2009; thus, we infer the approval spans high-grade astrocytoma and glioblastoma as currently classified.

#### 6.4.1.1 Key Recommendations for IV Anti-VEGF Therapies

While systemic therapy with bevacizumab is an option for the management of patients with recurrent or progressive high-grade[***] gliomas, efficacy of all approved treatment options, including bevacizumab, remains poor for recurrent disease.[12] Thus, enrollment into a clinical trial is the primary preferred approach for recurrent or progressive, high-grade gliomas over all current recommended options.[12] Otherwise, bevacizumab (or an FDA-approved biosimilar) is among preferred options as monotherapy, or among other-recommended combination regimens for glioblastoma, astrocytoma (IDH mutant, grade 3 or 4), or for oligodendroglioma (IDH mutant, 1p19Q co-deleted[†††], recurrent progressive disease, grade 3; **Table 12**). Systemic therapy with bevacizumab may also be considered for low-grade gliomas (WHO grade 1 or 2) that are unresectable or that recur following surgical resection. No other IV anti-VEGF therapies are recommended for gliomas.[12]

Unlike the 2023 NCCN guideline, the ASCO 2021 guideline did not include formal recommendations regarding bevacizumab use for recurrent gliomas, potentially because the supportive evidence did not show an improvement in overall survival with bevacizumab. However, authors expressed that because bevacizumab has a steroid-sparing effect, this option can improve patient quality of life. Considering this factor, and a possible benefit in progression-free survival, authors acknowledged that bevacizumab "retains a potentially important role in supportive care management of recurrent gliomas" (ASCO, page 17).[76]

[***] High grade gliomas are WHO grade 3 and 4 tumors; examples include glioblastoma IDH wildtype, WHO grade 4; astrocytoma IDH-mutant, WHO grade 3 or 4 ; oligodendroglioma (IDH-mutant, 1p19q codeleted), WHO grade 3

[†††] 1p19Q co-deleted means loss of short and long arm of a chromosome.

*Table 12. NCCN CNS Cancer Guideline, IV Anti-VEGF Treatment Recommendations, 2023* [10,a]

| **A. Glioblastoma Systemic Therapy Options for Recurrent or Progressive Disease** | |
|---|---|
| *Preferred regimens, category 2A:*<br>• **bevacizumab**<br>• regorafenib<br>• temozolomide (TMZ)<br>• carmustine or lomustine,<br>• procarbazine/lomustine/vincristine (PCV) | *Other recommended regimens, category 2A:*<br>• carmustine or lomustine + **bevacizumab**,<br>• TMZ/**bevacizumab** |
| **B. Systemic Therapy Options for**<br>**1. Recurrent or Progressive, WHO Grade 3 Oligodendroglioma[b] (IDH-mutant, 1p19q co-deleted), or**<br>**2. Recurrent, WHO Grade 3 or 4 Astrocytoma[b] (IDH-mutant)** | |
| *Preferred regimens, category 2A:*<br>• temozolomide (TMZ)<br>• carmustine/lomustine,<br>• **bevacizumab**<br>• procarbazine/lomustine/vincristine (PCV) | *Other recommended regimens, category 2A:*<br>• carmustine or lomustine + **bevacizumab**,<br>• TMZ/**bevacizumab** |

*Abbreviations: BEV, bevacizumab; CNS, central nervous system; IDH, isocitrate dehydrogenase; NCCN, National Comprehensive Cancer Network; TMZ, temozolomide*
*[a] A bevacizumab FDA-approved biosimilar may substitute for originator bevacizumab*
*[b] Options specified are for patients with good performance status (ie, scoring 60 or higher on the Karnofsky Performance Status scale for level of functional impairment, with higher scores reflecting less impairment). Evidence/Consensus Category 1: recommendation is based upon high-level evidence and a uniform NCCN consensus; Category 2A is based upon lower-level evidence, but with uniform NCCN consensus; Category 2B is based upon lower-level evidence, and majority consensus.*

## *6.4.2 Renal Cell Carcinoma (RCC)*

Kidney/renal pelvis cancer has the 9th highest cancer-diagnosis incidence rate in the US (age-adjusted rate: 15.8 per 100,000 people).[26] The majority (85%) of kidney tumors are renal cell carcinomas (RCC) and the majority of RCC cases (70%) are of clear cell histology (ccRCC).[11] RCC risk factors include smoking, obesity, and hypertension. RCC can also be hereditary, caused by genetic mutations in the von Hippel-Lindau (VHL) gene. The most common location of RCC metastasis are lung, bone, liver, lymph nodes, adrenal glands, and the brain. Genetic evaluation for RCC is recommended for patients who present with multiple renal masses, are 46 years old or younger at diagnosis, or have a family history of RCC.[11]

### 6.4.2.1 Key Recommendations for IV Anti-VEGF Therapies

The NCCN guideline specifies treatment regimens for RCC according to tumor histology and prognostic risk stratification.[11] Where bevacizumab is stated as an option, the NCCN considers an FDA-approved biosimilar to be substitutable. With respect to relapsed or metastatic ccRCC, bevacizumab monotherapy is among recommended subsequent-line options (ie, after failing a first line regimen), regardless of prior treatment (**Table 13**). For non-clear cell histology metastatic RCC (mRCC), bevacizumab is a listed option as monotherapy or in combination with everolimus (useful in certain circumstances). Additionally,

bevacizumab is recommended in combination with erlotinib for advanced papillary RCC disease (including hereditary liomyomatosis and RCC). No other IV anti-VEGF therapies are recommended for mRCC.[11]

*Table 13. NCCN Kidney Cancer Guideline, IV Anti-VEGF Treatment Recommendations, 2023*[11]

<table>
<tr><th colspan="3">Clear Cell RCC (ccRCC), Relapsed or Stage 4 Disease</th></tr>
<tr><th colspan="2">First-line Therapy</th><th>Subsequent-line Therapy</th></tr>
<tr>
<td>Preferred, category 1 (except cabozantinib, 2A):<ul><li>Axitinib/ pembrolizumab</li><li>Cabozantinib/ nivolumab</li><li>Lenvatinib/ pembrolizumab</li><li>Ipilimumab/ nivolumab (for P/I risk groups)</li><li>Cabozantinib (for P/I risk groups)</li></ul></td>
<td>Other recommended, category 2A (except cabozantinib, 2B):<ul><li>Axitinib/avelumab</li><li>Cabozantinib (for favorable risk group)</li><li>Ipilimumab/nivolumab (for favorable risk group)</li><li>Pazopanib</li><li>Sunitinib</li></ul>Useful in Certain Circumstances:<ul><li>Axitinib (category 2B)</li><li>High-dose IL-2</li><li>Temsiroliums (for P/I risk groups)</li></ul></td>
<td>Immuno-oncology Naïve, category 2A:<ul><li>Axitinib/pembrolizumab</li><li>Cabozantinib</li><li>Cabozantinib/nivolumab</li><li>Lenvatinib/everolimus or pembrolizumab</li><li>Ipilimumab/nivolumab</li><li>Nivolumab</li></ul>Prior Immuno-oncology, category 2A<ul><li>Axitinib</li><li>Cabozantinib</li><li>Lenvatinib/everolimus</li><li>Tivozanib</li></ul>Refer to guideline for additional options designated as useful in certain circumstances (eg, axitinib +/- pembrolizumab or avelumab, pazopanib, sunitinib, tivozanib bevacizumab, cabozantinib/nivolumab, among others)</td>
</tr>
<tr><th colspan="3">Systemic Therapy for Non-Clear Cell RCC (nccRCC), Relapsed or Stage 4 Disease</th></tr>
<tr>
<td>Preferred, category 2A:<ul><li>Clinical trial enrollment</li><li>Cabozantinib</li></ul></td>
<td>Other recommended, category 2A:<ul><li>Lenvatinib/everolimus</li><li>Nivolumab</li><li>Nivolumab/ cabozantinib</li><li>Pembrolizumab</li><li>Sunitinib</li></ul></td>
<td>Useful in Certain Circumstances, category 2A (except where indicated)<ul><li>Axitinib</li><li>Bevacizumab (eg, for papillary RCC)</li><li>Bevacizumab/erlotinib (for advanced papillary RCC, including HLRCC)</li><li>Bevacizumab/everolimus</li><li>Erlotinib</li><li>Everolimus</li><li>Nivolumab/ipilimumab (category 2B)</li><li>Pazopanib</li><li>Temsirolimus</li></ul></td>
</tr>
</table>

*Abbreviations: ccRCC, clear cell renal cell carcinoma; HLRCC, hereditary Leiomyomatosis and Renal Cell Carcinoma; NCCN, National Comprehensive Cancer Network; nccRCC, non-clear cell renal cell carcinoma; P/I, poor or intermediate; RCC, renal cell carcinoma*

*Evidence/Consensus Category 1: recommendation is based upon high-level evidence and a uniform NCCN consensus; Category 2A is based upon lower-level evidence, but with uniform NCCN consensus; Category 2B is based upon lower-level evidence, and majority consensus.*

*Note: oral anti-VEGF options in the guideline include axitinib, cabozantinib, lenvatinib, pazopanib, sunitinib, and tivozanib*

### 6.4.3 Cervical Cancer

Based on 2020 data, the incidence rate in the US of cervical cancer is 7 new cases and 2 deaths per 100,000 women.[26] A main risk factor for cervical cancer is persistent human papillomavirus (HPV) infection. The majority of cervical cancer cases are of squamous cell histology (80%) and 20% are adenocarcinomas.[77]

#### 6.4.3.1 Key Recommendations for IV Anti-VEGF Therapies

Bevacizumab is recommended as part of several NCCN preferred and alternative regimens (in combination with other chemotherapy agents (see **Table 14**) for first-line systemic therapy of cervical cancer including squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma.[13,77] Bevacizumab may also be used as monotherapy (other recommended regimen) as second-line or subsequent therapy for recurrent or metastatic disease of the previously mentioned histologies, in addition to cervical small cell neuroendocrine carcinoma. An FDA-approved biosimilar can be substituted for the originator bevacizumab. No other IV anti-VEGF therapies are recommended by the NCCN for cervical cancer.[13,77]

*Table 14. NCCN Cervical Cancer Guideline, IV Anti-VEGF Treatment Recommendations, 2023[13]*

- Consider chemoradiation (eg, platin-based therapies), or if disease is recurrent or metastatic consider systemic therapy as follows:

**First-line systemic therapy for squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma cervical cancer**

*Preferred regimens*:

- For PDL-1 positive tumors:
  - Pembrolizumab + cisplatin/paclitaxel ± **bevacizumab** for PD-L1–positive tumors (category 1)
  - Pembrolizumab + carboplatin/ paclitaxel ± **bevacizumab** for PD-L1– positive tumors (category 1)
- Cisplatin/paclitaxel/**bevacizumab** (category 1)
- Carboplatin/paclitaxel/**bevacizumab** (category 2A)

*Other Recommended Regimens*

- Cisplatin/paclitaxel (category 1)
- Carboplatin/paclitaxel, for patients on prior cisplatin treatment (category 1)
- Topotecan/paclitaxel/**bevacizumab** (category 1)
- Topotecan/paclitaxel (category 2A)
- Cisplatin/topotecan (category 2A)
- Cisplatin (category 2A)
- Carboplatin (category 2A)

*Refer to guideline for second-line or subsequent regimens (bevacizumab not among these)*

*Abbreviations: NCCN, National Comprehensive Cancer Network; PD-L1, programmed cell death 1 ligand*

*Evidence/Consensus Category 1: recommendation is based upon high-level evidence and a uniform NCCN consensus; Category 2A is based upon lower-level evidence, but with uniform NCCN consensus; Category 2B is based upon lower-level evidence, and majority consensus*

### *6.4.4 Ovarian/Fallopian Tube/Peritoneal Cancer*

Based on 2020 data, the US incidence rate of ovarian cancer is 9 new cases per 100,000 women. Ovarian cancer is attributed as the 5th leading cause of cancer-related death in US women, at a rate of 6 per 100,000.[26] Ovarian cancers are diverse in histopathology but most commonly are of epithelial type, accounting for about 90% of malignant ovarian cancers.[14] The main subtypes of epithelial ovarian cancer include serous (70% of epithelial ovarian cancers), endometrioid, clear cell, mucinous, and carcinosarcoma. Epithelial cancer has a 5-year survival rate of 49%. Nearly half of patients with this disease present with metastasis at diagnosis. Ovarian cancers that occur much less often than epithelial type include malignant sex cord-stromal tumors, and germ cell tumors.[14] Because epithelial ovarian cancer and peritoneal serous carcinoma may originate from the fallopian tube more often than initially realized, in addition to having similar histology and clinical features, they are often referred to collectively under the umbrella term of epithelial ovarian carcinoma (EOC).[78,79]

Screening for the following mutations informs treatment decisions and is recommended for patients after receiving a diagnosis of ovarian, fallopian tube, or primary peritoneal cancer: BRCA1/; or in the absence of BRCA mutation, loss of heterozygosity (LOH) or homologous recombination deficiency (HRD) status.[14] In the case of disease recurrence following treatment, tumor molecular analysis is also recommended when considering targeted pharmacotherapies; these may include but are not limited to BRCA1/2, HRD status, microsatellite instability (MSI), mismatch repair (MMR), tumor mutational burden (TMB), BRAF, FRα, RET, and NTRK.[14]

#### 6.4.4.1 Key Recommendations for IV Anti-VEGF Therapies

The NCCN describes that their "…recommendations are primarily based on data from patients with the most common subtypes—high-grade serous and grade 2 and 3 endometrioid carcinoma" (NCCN, page 66).[14] In general bevacizumab-containing regimens are options for all epithelial cancer types, either as (a) preferred or alternative regimens for primary therapy of stage II-IV disease, or (b) as recurrence therapy in preferred and alternative regimen options for platinum-sensitive disease (**Table 15**). Bevacizumab may also be used for recurrence therapy of malignant sex cord-stromal tumors (other recommended regimen). An FDA-approved biosimilar can be substituted for the originator bevacizumab.[14]

*Table 15. NCCN Epithelial Ovarian, Fallopian Tube, and Primary Peritoneal Cancer Guideline, IV Anti-VEGF Treatment Recommendations, 2023*[14]

**Primary Systemic Therapy:**

- **Bevacizumab-based regimens** (in combination with various chemotherapy agents) are among preferred and alternative regimens for **stage II-IV** disease of epithelial ovarian, fallopian tube, or primary peritoneal cancer of the following histologies: high-grade serous, endometrioid grade 2/3, clear cell carcinoma, carcinosarcoma, mucinous carcinoma, low-grade serous, and grade 1 endometrioid. (category 2A or 2B, depending on the histology subtype and regimen)

***Stage II, III, IV Post-primary Treatment:*** *for patients previously treated with bevacizumab as part of primary therapy:*

- **Bevacizumab** with olaparib (preferred, category 1), or with niraparib, is recommended as a maintenance therapy option (for disease with or without of BRAC1/2 mutation)
- **Bevacizumab** monotherapy is recommended as a maintenance therapy option in disease with BRAC1/2 WT or unknown status (category 2A)

**Recurrence Therapy:**

- **Bevacizumab** is among preferred, other recommended, and useful in certain circumstances regimens for the treatment of patients with disease recurrence (category 2A or 2B depending on the regimen)

*Abbreviations: NCCN, National Comprehensive Cancer Network*

*Evidence/Consensus Category 1: recommendation is based upon high-level evidence and a uniform NCCN consensus; Category 2A is based upon lower-level evidence, but with uniform NCCN consensus; Category 2B is based upon lower-level evidence, and majority consensus*

## 6.5 Indications Unique to Ramucirumab: Esophagogastric & Gastric Cancer

In 2021, gastric cancer ranked 16th for most commonly diagnosed cancer and 17th for leading cause of cancer-related death in the US.[80] Based on 2020 data, US incidence rates per 100,000 people were 6 new gastric cancer cases, 4 new esophageal cancer cases, 3 gastric cancer-related deaths, and 4 esophageal cancer-related deaths.[26]

Of the IV anti-VEGF therapies, only ramucirumab is FDA-approved for gastric or gastro-esophageal junction adenocarcinomas (see **Table 16**).

*Table 16. Indications Unique to Ramucirumab[3]*

| |
|---|
| **Gastric or gastro-esophageal junction (GEJ) adenocarcinoma** (advanced or metastatic) with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy<br>• 8 mg/kg every 2 weeks as a single agent or in combination (ie, administered prior to) with weekly paclitaxel |

### *6.5.1 Key Recommendations for IV Anti-VEGF Therapies*

Ramucirumab is the only anti-VEGF therapy recommended among NCCN guidelines for the treatment of esophageal, gastro-esophageal junction (GEJ), or gastric cancers (does not include gastrointestinal stromal cancer). In particular, ramucirumab is recommended as second-line or subsequent therapy (as monotherapy or part of chemotherapy combination regimens) for unresectable, locally advanced, recurrent, or metastatic gastric, esophageal, or GEJ adenocarcinoma.[80,81] Ramucirumab is not a biomarker directed therapy as are other targeted therapies that are part of other preferred or alternative regimen options (eg, trastuzumab for HER2 overexpression; PD-1 inhibitors, pembrolizumab/nivolumab, entrectinib/larotrectinib, selpercatinib, and dabrafenib/trametinib for PD-L1 expression). See **Table 17** for NCCN guideline recommendations for IV anti-VEGF therapy for gastric and esophageal cancer.

The ASCO 2023 guideline on gastroesophageal cancer also recommends ramucirumab with paclitaxel for subsequent therapy in patients with gastroesophageal (including gastric) or GEJ adenocarcinoma cancers—similar to the NCCN guideline.[82]

### *6.5.2 Comparative RCTs*

There are no head-to-head studies of IV-anti-VEGF therapy among treatment guidelines, and there is at least 1 SR also showing no IV-anti VEGF head-to-head RCTs (2018).[83]

*Table 17. NCCN Gastric and Esophageal Cancer Guidelines, IV Anti-VEGF Treatment Recommendations 2023*

| NCCN Guideline for Gastric Cancer[80] |
|---|
| **Second-line or subsequent therapy** for unresectable locally advanced, recurrent, or metastatic disease where local therapy is not indicated<br>• *Preferred regimens*<br>  ○ **ramucirumab/**paclitaxel (category 1)<br>  ○ fam-trastuzumab deruxtecan for HER2 positive adenocarcinoma (category 2A)<br>  ○ monotherapy with docetaxel, paclitaxel, or irinotecan (category 1)<br>  ○ fluorouracil/irinotecan (category 2A)<br>  ○ trifluridine/tipiracil for third-line or subsequent therapy (category 1)<br>• Other recommended regimens<br>  ○ **ramucirumab** (category 1)<br>  ○ **ramucirumab**/irinotecan (category 2A)<br>  ○ **ramucirumab**/fluorouracil/irinotecan (category 2A)<br>  ○ irinotecan/cisplatin (category 2A)<br>  ○ docetaxel/irinotecan (category 2B)<br>• *Useful in certain circumstances*: entrectinib or larotrectinib for NTRK fusion positive, pembrolizumab for MSI-H, dMMR, TMB high, dostarlimab for MSI-H or dMMR, dabrafenib/trametinib for BRAF V600E, selpercatinib for RET positive (category 2A for all regimens in list) |
| **NCCN Guideline for Esophageal or Esophagogastric Junction (GEJ) Cancers[81]** |
| **Second-line or subsequent therapy for adenocarcinoma** (unresectable locally advanced, recurrent, or metastatic adenocarcinoma where local therapy is not indicated<br>• *Preferred regimens*<br>  ○ **ramucirumab/**paclitaxel (category 1 for GEJ or 2A for esophageal location)<br>  ○ fam-trastuzumab deruxtecan for HER2 positive adenocarcinoma (category 2A)<br>  ○ monotherapy with docetaxel, paclitaxel, or irinotecan (category 1)<br>  ○ fluorouracil/irinotecan (category 2A)<br>  ○ trifluridine/tipiracil for third-line or subsequent therapy for GEJ<br>• *Other recommended regimens*:<br>  ○ **ramucirumab** (category 1 for GEJ or 2A for esophageal location)<br>  ○ **ramucirumab**/irinotecan (category 2A)<br>  ○ **ramucirumab**/fluorouracil/irinotecan (category 2A)<br>  ○ irinotecan/cisplatin (category 2A)<br>  ○ docetaxel/irinotecan (category 2B)<br>• *Useful in certain circumstances*: entrectinib or larotrectinib for NTRK fusion positive, pembrolizumab for MSI-H, dMMR, TMB high, dostarlimab for MSI-H or dMMR, dabrafenib/trametinib for BRAF V600E, selpercatinib for RET positive (category 2A for all regimens in list) |

*Abbreviations: GEJ, esophagogastric junction; NCCN, National Comprehensive Cancer Network*

*Evidence/Consensus Category 1: recommendation is based upon high-level evidence and a uniform NCCN consensus; Category 2A is based upon lower-level evidence, but with uniform NCCN consensus; Category 2B is based upon lower-level evidence, and majority consensus*

# 7.0 OFF-LABEL USES

**Table 18** compiles the recommended uses (applicable for Micromedex only) and/or evidence ratings that Micromedex and Lexicomp provide for *recognized* off-label uses. There are many uses for which Micromedex recommends bevacizumab (either as level IIa recommendation [recommended for most cases] or IIb [recommended for some cases]). Micromedex lists only 1 off-label use for ramucirumab and none for ziv-aflibercept. While Lexicomp includes a substantially smaller list of off-label uses for bevacizumab, it provides the extra detail of support by at least one evidence-based clinical practice guideline (denoted as G in the table). Lexicomp lists 1 off-label use for ziv-aflibercept and none for ramucirumab.

Additional off-label uses for bevacizumab (potentially unaccounted for in Micromedex/Lexicomp) that appear to have positive evidence, which we have come across during the literature search and/or review of NCCN guidelines, are as follows:

- Bevacizumab has been studied for small intestinal adenocarcinoma[84] and small bowel adenocarcinoma;[85] it is recommended among the NCCN guideline for small bowel adenocarcinoma[86]
- Malignant sex cord-stromal tumors: NCCN 2023 guideline includes bevacizumab as an “other recommended” regimen for recurrence therapy[14]
- Intracranial and spinal ependymoma: NCCN 2023 guideline incudes bevacizumab as an “other recommended” regimen for certain patients with recurrent disease[12]
- Meningiomas: NCCN 2023 guideline incudes bevacizumab as a recommended regimen[12]
- Bevacizumab is among NCCN preferred regimens for grade 3 astrocytoma (IDH mutant), recurrent or progressive, grade 3 oligodendroglioma (IDH mutant, 1p19Q co-deleted), or low-grade gliomas (WHO grade 1 or 2) that are unresectable or that recur following surgical resection[12]
- Bevacizumab in combination with trifluridine +/- tipiracil is an NCCN recommended option for subsequent therapy in mCRC[8]
- Bevacizumab for first-line systemic therapy of cervical cancer in combination regimens with pembrolizumab, and/or carboplatin/paclitaxel; or as monotherapy in subsequent therapy for recurrent or metastatic cervical cancer (NCCN guideine[77])

Additional off-label uses for ramucirumab and ziv-aflibercept (unaccounted for in Micromedex/Lexicomp) that appear to have positive evidence based on NCCN guidelines are as follows:

- Ramucirumab or ziv-aflibercept in combination with irinotecan only for subsequent therapy of advanced or metastatic CRC: NCCN 2023 guideline for CRC[8]
- The approved indication for ramucirumab and mCRC specifically refers to ramucirumab application after having failed prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine;[3] however, the NCCN guideline does not require failure of this particular regimen, placing ramucirumab as a subsequent therapy option after failure of any NCCN recommended initial regimens.[8]
- The NCCN guidelines appear broader than labeled indications which respect to allowable prior/failed therapies before using the following agents for subsequent therapy (patients may fail other first-line guideline recommended therapies): (a) ziv-aflibercept for mCRC[8], and (b) ramucirumab for HCC or NSCLC subsequent therapy[10]

*Table 18. Off-Label Uses of Intravenous Anti-VEGF Therapies*

| Micromedex[a,b,18] | Lexicomp[b,c,19] |
|---|---|
| **Bevacizumab** | |
| *Effective (Category A):*<br>• Malignant mesothelioma of pleura, unresectable disease (first-line therapy, in combination with pemetrexed and cisplatin) (IIa)<br>*Evidence favors efficacy (Category B):*<br>• Metastatic colorectal cancer (first-line therapy, in combination with oxaliplatin/capecitabine) (IIb)<br>• Metastatic colorectal cancer, in previously untreated elderly patients, ineligible for oxaliplatin- or irinotecan-based chemotherapy (IIa)<br>• Metastatic colorectal cancer, advanced, relapsed (in combination therapy) (IIb)<br>• Nonsquamous non-small cell lung cancer, Stage IIIB/IV, continuation maintenance therapy as monotherapy following platinum-based, first-line therapy (IIa)<br>• Nonsquamous non-small cell lung cancer, Stage IIIB/IV, first-line therapy in combination with pemetrexed/carboplatin (IIb)<br>• Gastric cancer, advanced (first-line therapy in combination with fluoropyrimidine-based regimen) (IIb)<br>• Liver carcinoma, advanced (IIb)<br>• Metastatic renal cell carcinoma, as monotherapy or in combination therapy (IIb)<br>• Metastatic breast cancer, HER2-negative (as first-line or second-line therapy, in combination with chemotherapy) (IIb) | • Age-related macular degeneration (**LOE A, G**; American Academy of Ophthalmology)<br>• Diabetic macular edema (**LOE A, G**; American Academy of Ophthalmology)<br>• Breast cancer, metastatic (LOE B)<br>• Endometrial cancer, recurrent or persistent (LOE B)<br>• Hereditary hemorrhagic telangiectasia (LOE C, **G**; American College of Gastroenterology)<br>• Malignant pleural mesothelioma, unresectable (**LOE A, G**; American Society of Clinical Oncology)<br>• Soft tissue sarcoma, angiosarcoma or hemangiopericytoma (LOE C) |



*Abbreviations: LOE, level of evidence; RCTs, randomized controlled trials*

*[a] Non-FDA uses were extracted from Micromedex that were rated as "effective" or "evidence favors efficacy"; note that some off-label uses are viewable in the "In-depth Answers" view but not in the "Quick Answers" view of the database.*

- *Micromedex Categories for Strength of Evidence: **Category A** is based on meta-analyses of homogenous RCT results, or multiple, well-designed RCTs with large patient population; **Category B** is based on data from meta-analyses of RCTs with either incongruent effect estimates, small populations, significant methodological flaws, or nonrandomized studies.*
- *Micromedex Strength of Recommendation: **IIa**, recommended in most cases; **IIb** recommended in some cases*

*[b] All listed off-label uses are specified for the adult population with the exception of bevacizumab for retinopathy associated with prematurity*

*[c] LexiComp Level of Evidence Definitions:*

- *B - Evidence from RCT(s) with important limitations, or very strong evidence of some other research design. Estimate of effect may change with future evidence.*
- *C - Evidence from observational studies, unsystematic clinical experience, or from potentially flawed. Estimate of effect is uncertain.*
- *G - Use has been substantiated by inclusion in at least one evidence-based or consensus-based clinical practice guideline.*

*Table 18. Off-Label Uses of Intravenous Anti-VEGF Therapies*

| Micromedex[a,b,18] | Lexicomp[b,c,19] |
|---|---|
| • Metastatic breast cancer, in combination with capecitabine in patients previously treated with an anthracycline and a taxane (IIb)<br>• Age related macular degeneration - Choroidal retinal neovascularization (IIa)<br>• Angioid streaks of choroid – Chorodial retinal neovascularization (IIb)<br>• Macular edema due to diabetes mellitus (IIb)<br>• Branch retinal vein occlusion with macular edema (IIb)<br>• Central retinal vein occlusion with macular edema (IIb)<br>• Choroidal retinal neovascularization, secondary to pathologic myopia (IIb)<br>• Neovascular glaucoma, adjunct (IIb)<br>• Retinopathy due to diabetes mellitus (IIa) or due to prematurity (pediatric) (IIb)<br>• Bleeding from nose - Osler hemorrhagic telangiectasia syndrome (IIb)<br>• Necrosis of central nervous system due to exposure to ionizing radiation (IIb) | |
| **Ramucirumab** | |
| *Evidence favors efficacy (Category B):*<br>• Urothelial carcinoma, metastatic or advanced, with progression after platinum-containing chemotherapy (IIb) | *None listed* |
| **Ziv-aflibercept** | |
| *None listed* | • Ascites, symptomatic due to malignant ovarian cancer (LOE C) |



*Abbreviations: LOE, level of evidence; RCTs, randomized controlled trials*

*[a] Non-FDA uses were extracted from Micromedex that were rated as "effective" or "evidence favors efficacy"; note that some off-label uses are viewable in the "In-depth Answers" view but not in the "Quick Answers" view of the database.*

- *Micromedex Categories for Strength of Evidence: **Category A** is based on meta-analyses of homogenous RCT results, or multiple, well-designed RCTs with large patient population; **Category B** is based on data from meta-analyses of RCTs with either incongruent effect estimates, small populations, significant methodological flaws, or nonrandomized studies.*
- *Micromedex Strength of Recommendation: **IIa**, recommended in most cases; **IIb** recommended in some cases*

*[b] All listed off-label uses are specified for the adult population with the exception of bevacizumab for retinopathy associated with prematurity*

*[c] LexiComp Level of Evidence Definitions:*

- *B - Evidence from RCT(s) with important limitations, or very strong evidence of some other research design. Estimate of effect may change with future evidence.*
- *C - Evidence from observational studies, unsystematic clinical experience, or from potentially flawed. Estimate of effect is uncertain.*
- *G - Use has been substantiated by inclusion in at least one evidence-based or consensus-based clinical practice guideline.*

# 8.0 COMPARATIVE EVIDENCE

Upon a literature search for direct, head-to-head randomized controlled trial (RCT) evidence, with respect to FDA-indicated disease states in common between the IV anti-VEGF therapies (ie, mCRC, HCC, or NSCLC), no RCTs were found that compared bevacizumab, ramucirumab, or ziv-aflibercept. Many SRs identified were open to comparative studies of interest, however, they did not find any, as further detailed below in subsection 8.2. This is likely because these agents are often used in differing lines of therapy across disorders, related to how they were studied/developed. On the other hand, limited comparative evidence was identified among 3 recent systematic reviews (SRs) with comparisons of certain bevacizumab biosimilars to the originator; RCTs were in the setting of mCRC or for non-squamous NSCLC. Overall, there were no remarkable differences in efficacy identified between the biosimilars versus the originator bevacizumab for these indications. This finding is in line with the general FDA description of biosimilars as having "…no clinically meaningful differences in terms of safety, purity, and potency (safety and effectiveness) from an existing FDA-approved biologic [reference product]…" with respect to the approved indication (FDA.gov).[87]

## 8.1 Bevacizumab Originator vs. Biosimilars

Three SRs were identified that searched for and reported RCTs of bevacizumab (Avastin) vs. biosimilars in the setting CRC (1 SR) or non-squamous NSCLC (3 SRs).[15-17] One comparative RCT in patients with NSCLC is available for each of the 3 US-approved biosimilars (Zirabev, Mvasi, and Alymsys[‡‡‡]). Based on information reported in the SRs, individual results of the included RCTs show no significant differences between bevacizumab and these 3 biosimilars with respect to the following outcomes:

- objective response rate[15,16]
- progression free survival [16]
- overall survival [15,16]
- incidence of grade 3-5 adverse events[15]

Similarly, meta-analysis effect estimates for the above outcomes (which also included data of additional biosimilars available in other countries, along with data for US biosimilars) resulted in no significant differences for biosimilars altogether vs. originator bevacizumab.[15,16]

One RCT is available in the mCRC population, which compared bevacizumab to the biosimilar, Alymsys. No significant difference was found for objective response or incidence of grade 3-5 adverse events.[17]

## 8.2 SRs for mCRC, HCC, and NSCLC

***In the Setting of mCRC**:* Consistent with the NCCN and ASCO guidelines, which are absent of head-to-head IV anti-VEGF comparative RCTs, several recent SRs (published in 2023 and 2022) also show that there are no head-to-head studies of between bevacizumab,[30] ramucirumab,[31,32] or ziv-aflibercept[33] containing regimens for the treatment of mCRC.[34] Additional SRs published in 2021 also show no head-to-head trials for first-line systemic treatment for mCRC[35,36] and/or second-line treatment.[37,38]

[‡‡‡] In the included SRs, the biosimilars are referred to as their study names: Alymsys is MB02, Mvasi is ABP215, and Zirabev is PF06439535

***In the Setting of HCC:*** Consistent with the guidelines, which are absent of direct head-to-head IV anti-VEGF comparative studies, several recent SRs (from 2023 and 2022) also show that there are no head-to-head RCTs of bevacizumab- or ramucirumab-containing regimens for the treatment of advanced hepatocellular carcinoma. Moreover, we would not expect bevacizumab and ramucirumab to be compared since one (bevacizumab) is established for first-line systemic treatment and the other (ramucirumab) is established only for subsequent therapy. In particular, SRs addressed the following treatment areas and show no IV anti-VEGF head-to-head studie:

- first-line[49-54] or second-line[55] systemic treatment for advanced HCC[56]
- novel combination strategies for unresectable HCC[57]
- immune checkpoint inhibitor combinations in advanced HCC[42]

***In the Setting of NSCLC:*** Consistent with the NCCN guideline, which is absent of head-to-head IV anti-VEGF comparative RCTs, several recent SRs (from 2023 and 2022) also show that there are no head-to-head studies of between bevacizumab- or ramucirumab-containing regimens for the treatment of advanced or metastatic NSCLC; SRs address the following treatment areas:

- first-line immune checkpoint inhibitor regimens for advanced NSCLC[61-64]
- first-line therapies in EGFR-mutated advanced NSCLC [65-69]
- advanced NSCLC with negative PD-L1 expression[70]
- first-line treatments for NSCLC with high programmed death ligand-1 expression[71]
- immunotherapy with chemotherapy versus bevacizumab with chemotherapy for first-line treatment of driver-gene negative NSCLC[72]

# 9.0 SAFETY

## 9.1 Warnings and Precautions

**Table 19** outlines the warnings/precautions labeled for the IV anti-VEGF therapies, with elaborations for each provided after the table. Anti-VEGF therapies share many warnings in common. As a class, they slow/impair wound healing and may be associated with a small, elevated risk for hemorrhage, GI perforation, thromboembolic events, hypertension, proteinuria, and a neurologic disorder called posterior reversable encephalopathy syndrome. A warning regarding infusion reactions, some potentially severe, is specified for bevacizumab and ramucirumab. While each agent had neutropenia reported as common adverse event and numerically higher than the comparator group (for a particular cancer population/regimen; see *Adverse Events* section 9.2) a warning regarding neutropenia and related complications is labeled only for ziv-aflibercept; however, the clinical precaution should also be considered for the others.[1-7]

*Table 19. Labeled Warnings for IV Anti-VEGF Therapies*[1-7]

| Warning | Bevacizumab and Biosimilars | Ramucirumab | Ziv-aflibercept |
|---|---|---|---|
| Gastrointestinal Perforation | X | X | X |
| Fistula | X | | X |
| Impaired Wound Healing | X | X | X |
| Increased Hemorrhage Risk | X | X | X |
| Thromboembolic Events | X | X | X |
| Hypertension | X | X | X |
| Posterior Reversible Encephalopathy Syndrome[a] | X | X | X |
| Proteinuria/ Renal Injury | X | X | X |
| Embryo-fetal Toxicity | X | X | X |
| Impaired Fertility and/or Ovarian Failure | X | X | X |
| Infusion-Related Reactions | X | X | |
| Congestive Heart Failure Risk When Combined with Anthracyclines | X | | |
| Worsening Hepatic Impairment | | X | |
| Thyroid Dysfunction | | X | |
| Neutropenia | No labeled warning but neutropenia was a common adverse event for certain cancers/regimens, also warranting caution | | X |

[a] *Also known as Reversible Posterior Leukoencephalopathy Syndrome*

***Gastrointestinal Perforations:*** *Discontinue bevacizumab, ramucirumab, and ziv-aflibercept upon development of gastrointestinal perforation.*

- Bevacizumab, ramucirumab, and ziv-aflibercept can increase the risk of gastrointestinal (GI) perforation, events which can be serious and life-threatening. Perforations occurred in clinical trials of various cancers at an incidence of incidence of 0.3% to 3% with bevacizumab, <1% to 2% with ramucirumab, and 0.8% with ziv-aflibercept. With bevacizumab treatment, higher incidence rates occur in patients with prior pelvic radiation. Patients should be monitored for signs and symptoms of GI perforation and the drug discontinued in the event of GI perforation. [1-7]

***Fistula:*** *Discontinue bevacizumab and ziv-aflibercept upon development of fistula formation in any organ.*

- Bevacizumab and ziv-aflibercept can increase the risk of fistula formation involving gastrointestinal and non-gastrointestinal sites. Serious fistula occurred in bevacizumab-treated patients at an incidence ranging from < 1% to 1.8% across clinical studies, and incidence was highest in patients with cervical cancer. Fistulas occurred with ziv-aflibercept in 1.5% of treated patients.[1-7]

***Surgery and Wound Healing Complications:*** *Anti-VEGF therapies can slow/impair wound healing.*

- Pause anti-VEGF treatment in the event of wound healing complications during anti-VEGF treatment, until the wound is adequately healed. They should be withheld for at least 28 days prior to elective surgery and should be avoided for at least 2 weeks (for ramucirumab) or 28 days (for bevacizumab and ziv-aflibercept) following a major surgery, and until adequate wound healing.[1-7]

***Hemorrhage:*** *Anti-VEGF therapies are associated with increased risk of hemorrhages*

- Severe or fatal hemorrhagic events have occurred in patients treated with anti-VEGF therapy. These agents should not be administered in patients with severe bleeding (eg, grade 3 or 4). Labeling for bevacizumab advises against use in patients with recent hemoptysis.[1-7]

***Arterial Thromboembolic Events (ATEs):*** *Risk of ATEs*

- Serious, sometimes fatal, ATEs occurred in patients treated with IV anti-VEGF therapies. The incidence of Grades 3-5 ATE was 5% and <1-2% in patients receiving bevacizumab or ramucirumab, respectfully. Grades 3-4 ATE occurred in 1.8% of patients treated with ziv-aflibercept.[1-7]

***Venous Thromboembolic Events (VTEs):*** *Risk of VTEs*

- Bevacizumab (but not others) has a warning for increased risk of VTEs. Grades 3-4 VTE occurred in 5% and 11% of patients on bevacizumab in 2 clinical trials, respectively, compared to 5% and 2% of patients on chemotherapy alone.[1-7]

***Hypertension:*** *Anti-VEGF therapies increase the risk of hypertension*

- Monitor blood pressure every 2 to 3 weeks or more frequently as clinically indicated. Treat with antihypertensive therapy if appropriate and continue monitoring blood pressure regularly. Withhold anti-VEGF treatment if not medically controlled; may resume once controlled (consider lower dosages per package insert). Discontinue for hypertensive crisis or hypertensive encephalopathy.[1-7]

***Posterior Reversible Encephalopathy Syndrome (PRES;*** *also known as reversible posterior leukoencephalopathy syndrome):* *Anti-VEGF therapies are associated with a small risk for PRES*

- PRES was reported in < 0.1% to 0.5% of patients across clinical studies with bevacizumab, ramucirumab, and ziv-aflibercept. The onset of symptoms is variable, occurring hours to months after initiation. PRES is a neurological disorder characterized by headache, seizure, lethargy, confusion, blindness, and other visual, neurologic, or possible hemodynamic disturbances. Magnetic resonance imaging is necessary to confirm the diagnosis of PRES. The anti-VEGF agent should be discontinued upon a diagnosis of PRES.[1-7]

***Renal Injury and Proteinuria****: IV Anti-VEGF therapies are associated with a small risk for proteinuria*

- Monitor urine protein and pause therapy with proteinuria ≥2 grams/24 hours; may resume once normalized. Discontinue anti-VEGF therapy in the event of nephrotic syndrome.[1-7]

***Infusion-Related Reactions:*** *Bevacizumab and ramucirumab have warnings regarding a small risk for infusion reactions*

- Premedicate prior to ramucirumab administration (see package insert for details). Monitor for symptoms during the infusion of these medications (bevacizumab or ramucirumab) in a setting with resuscitation equipment readily available. In the event of a hypersensitivity reaction during infusion, decrease the infusion rate for a mild reaction or pause therapy for moderate reactions and may resume at a lower rate once recovered. Discontinue IV anti-VEGF with severe infusion-related reactions and administer supportive medical therapy as needed.[2,3]

***Embryo-Fetal Toxicity:*** *Anti-VEGF therapy can cause fetal harm*

- Mechanism-of-action and animal studies implicate angiogenesis involving VEGF and VEGFR2 in critical aspects of reproduction, embryo-fetal development, and postnatal development. Animal models have demonstrated fetal harm (congenital malformations) with bevacizumab used at the clinical dose (10 mg/kg), as well as embryotoxic/teratogenic effects with ziv-aflibercept at low exposure levels (4 mg/kg). Ramucirumab has not been studied in animal embryo-fetal studies. Pregnant women should be advised of the potential risk to a fetus. Females with reproductive potential should use reliable contraception while using these agents and in following months after their discontinuation for the duration specified by the prescribing information (eg, 1-6 months depending on the agent). [1-7]

***Impaired Fertility/Ovarian Failure:*** *Advise patients of potential impairment of fertility with anti-VEGF therapy*

- Warnings for ovarian failure and/or impairment of fertility are stated in package inserts for bevacizumab and ziv-aflibercept. At exposures similar to the therapeutic exposure for humans, animal studies showed inhibitory effects of bevacizumab and ziv-aflibercept on ovarian function and follicular development (in addition to alterations in sperm morphology in animal studies with ziv-aflibercept). While less information is provided with respect to ramucirumab labeling, females of reproductive potential should be warned that the medication can impair fertility.[1-7]

***Congestive Heart Failure (CHF) with Bevacizumab:*** Bevacizumab increases the risk of CHF in combination with anthracycline-based chemotherapy

- Avoid use of bevacizumab with anthracycline-based chemotherapy since this combination is associated with a higher risk for developing CHF. In general, bevacizumab should be discontinued in the event of CHF development.[2]

***Worsening of Pre-existing Hepatic Impairment with Ramucirumab:*** *Ramucirumab is associated with worsening hepatic impairment symptoms*

- Treatment with ramucirumab was associated with new onset or worsening encephalopathy, ascites or hepatorenal syndrome in patients with Child-Pugh B or C cirrhosis. Worsening symptoms have also occurred in patients with Child-Pugh A cirrhosis. Use ramucirumab only if the potential benefits are judged to outweigh the risks of clinical deterioration. [1-7]

***Thyroid Dysfunction with Ramucirumab****: Monitor thyroid function with ramucirumab treatment*

- Grade 1-2 hypothyroidism occurred in <1-3% of treated patients in clinical trials.[3]

***Neutropenia and Neutropenic Complications with Ziv-aflibercept**: Delay administration of ziv-aflibercept until neutrophil count is 1.5 × $10^9$/L or higher*

- More patients with mCRC who were treated with the combination of ziv-aflibercept/FOLFIRI experienced Grade 3-4 neutropenic-related events neutropenia compared to patients in the control arm with placebo/FOLFIRI: 7% incidence difference between treatment groups for neutropenia, 2% difference for febrile neutropenia, and 0.3% difference for neutropenic infection/sepsis.[7]

## 9.2 Common Adverse Events

A summary of the most common adverse events reported in package inserts are summarized in the bullets below, specified according to the disease setting and whether use was in combination with another anti-cancer agent.

**Bevacizumab[2]**

- Adverse events occurring with an incidence >10% (assumed across all clinical trials, per package insert information) were nausea, vomiting, dehydration, sensory neuropathy, epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, hemorrhage, lacrimation disorder, back pain and exfoliative dermatitis
- Additional high-grade adverse reactions occurring in ≥20% of treated patients were also extracted from the clinical studies section of the package insert (for overlapping indications with other IV anti-VEGF agents):
  - For mCRC, in combination with FOLFIRI, (Grade 3-4 adverse events with an incidence ≥20% and 2% or more difference from placebo/IFL arm): leukopenia, neutropenia
  - For non-squamous NSCLC, in combination with paclitaxel/carboplatin (Grade 4-5 adverse event with an incidence ≥20% and 2% or more difference from paclitaxel/carboplatin arm): neutropenia

**Ramucirumab[3]**

- Gastric cancer setting, as monotherapy (incidence ≥10% and ≥2% higher than placebo): hypertension and diarrhea
- HCC setting, as monotherapy agent (incidence ≥15% and ≥2% higher than placebo): fatigue, peripheral edema, hypertension, abdominal pain, decreased appetite, proteinuria, nausea, and ascites. The most common laboratory abnormalities (incidence ≥30%) were thrombocytopenia, hypoalbuminemia, and hyponatremia.
- Gastric or GEJ cancer setting, in combination with paclitaxel (incidence ≥30% and ≥2% higher than placebo/paclitaxel): fatigue/asthenia, neutropenia, diarrhea, and epistaxis
- For NSCLC, in combination with erlotinib (incidence ≥30% and ≥2% higher than placebo/erlotinib): infections, hypertension, stomatitis, proteinuria, alopecia, and epistaxis, increased alanine, aminotransferase, increased aspartate aminotransferase, anemia, thrombocytopenia, and neutropenia
- For NSCLC, in combination with docetaxel (incidence ≥30% and ≥2% higher than placebo/docetaxel): neutropenia, fatigue/asthenia, and stomatitis/mucosal inflammation
- For mCRC, in combination with FOLFIRI (incidence ≥30% and ≥2% higher than placebo/FOLFIRI): diarrhea, neutropenia, decreased appetite, epistaxis, and stomatitis

**Ziv-aflibercept**[7]

- mCRC setting, in combination with FOLFIRI (≥20% incidence): leukopenia, diarrhea, neutropenia, proteinuria, AST increased, stomatitis, fatigue, thrombocytopenia, ALT increased, hypertension, weight decreased, decreased appetite, epistaxis, abdominal pain, dysphonia, serum creatinine increased, and headache.

# REFERENCES


1. Alymsys (bevacizumab-maly) injection solution. Package Insert. Amneal Pharmaceuticals LLC; April 2022.

2. Avastin (bevacizumab) for intravenous use. Package Insert. Genentech Inc.; September 2022.

3. Cyramza (ramucirumab) for intravenous use. Package Insert. Eli Lily and Company; March 2022.

4. Mvasi (bevacizumab-awwb) injection for intravenous use. Package Insert. Amgen Inc.; February 2023.

5. Vegzelma (bevacizumab-adcd) injection for intravenous use. Package Insert. CELLTRION Inc; September 2022.

6. Zirabev (bevacizumab-bvzr) injection for intravenous use. Package Insert. Pfizer Inc.; February 2023.

7. Zaltrap (ziv-aflibercept) for intravenous use. Package Insert. Sanofi-Aventis US LLC; December 2020.

8. Benson A, Venook A, Adam M, Al-Hawary M, Chen Y-J, Ciombor K, Cohen S. NCCN Guidelines: Colon Cancer, Version 4.2023. *NCCN Clinical Practice Guidelines in Oncology*. 2023, Accessed November 28, 2023. Available at https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf

9. Benson A, D'Angelica M, Abrams T, Abbott D, Ahmed A, Anaya D, Anders R. NCCN Guidelines Hepatocellular Carcinoma Version 2.2023 *NCCN Clinical Practice Guidelines in Oncology*. 2023, Accessed November 3, 2023. Available at https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1514

10. Ettinger D, Wood D, Riely G, et al. NCCN Guidelines: Non-Small Cell Lung Cancer, Version 1.2024. *National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®)*. Accessed January 9, 2024. Available at https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1450

11. Motzer R, Jonasch E, Agarwal N, et al. NCCN Guidelines: Kidney Cancer, Version 2.2024 *NCCN Clinical Practice Guidelines in Oncology*. 2023,

12. Nabors L, Portnow J, Baehring J, et al. NCCN Guidelines Version 1.2023 Central Nervous System Cancers. *National Comprehensive Cancer Network*. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

13. Abu-Rustum N, Yashar C, Arend R, et al. NCCN Guidelines Cervical Cancer Version 1.2024. *NCCN Clinical Practice Guidelines in Oncology*. 2023,

14. Armstrong D, Alvarez R, Backes F, Barroilhet L, Behbakht K, Berchuck A, Chen L-m. NCCN Guidelines Version 1.2024 Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer. *NCCN Clinical Practice Guidelines in Oncology*. 2024,

15. Yang L, Liu M, Cao X, Li N, Zheng B, Deng J, Cai H. Efficacy and safety of adding bevacizumab biosimilar or original drug to platinum-based chemotherapy as first-line treatment in patients with advanced NSCLC: a systematic review and meta-analysis. *Ther Adv Med Oncol*. 2022;14:17588359221130501. doi:10.1177/17588359221130501

16. Xiao X, Zhang G, Sun B, Wang C, Wang X, Kong F, Jia Y. Comparison of efficacy and safety of bevacizumab biosimilar and original bevacizumab in non-squamous non-small cell lung cancer: a systematic review and meta-analysis. *Transl Cancer Res*. 2022;11(6):1472-1482. doi:10.21037/tcr-22-71

17. Xu X, Zhang S, Xu T, Zhan M, Chen C, Zhang C. Efficacy and Safety of Bevacizumab Biosimilars Compared With Reference Biologics in Advanced Non-small Cell Lung Cancer or Metastatic Colorectal Cancer Patients: A Network Meta-Analysis. *Front Pharmacol*. 2022;13:880090. doi:10.3389/fphar.2022.880090

18. Merative. Micromedex DRUGDEX, Drug Monographs, Non-FDA Uses (In-depth Answers). Merative Micromedex.com; 2023.

19. Drug Monographs (Lexi-Drugs): Uses, Off-label. Lexicomp.com,; 2023. Accessed May 17, 2022. Available at http://online.lexi.com

20. Lefebvre C, Glanville J, Briscoe S, et al. Technical Supplement to Chapter 4: Searching for and selecting studies. In: Higgins J, Thomas J, Chandler J, Cumpston MS, Li T, Page MJ, VA W, eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 6.3 (updated February 2022)*. Cochrane; 2022. Available at www.training.cochrane.org/handbook

21. Lefebvre C, Manheimer E, Glanville J. Chapter 6.3. Planning the search process. In: Higgins J, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions, Version 5.1.0* The Cochrane Collaboration; 2011. Available at https://handbook-5-1.cochrane.org/

22. Ellis LM, Hicklin DJ. VEGF-targeted therapy: mechanisms of anti-tumour activity. *Nat Rev Cancer*. 2008;8(8):579-591. doi:10.1038/nrc2403

23. Weinberg BA, Hartley ML, Salem ME. Precision Medicine in Metastatic Colorectal Cancer: Relevant Carcinogenic Pathways and Targets-PART 1: Biologic Therapies Targeting the Epidermal Growth Factor Receptor and Vascular Endothelial Growth Factor. *Oncology (Williston Park)*. 2017;31(7):539-548.

24. Shibuya M. Vascular Endothelial Growth Factor (VEGF) and Its Receptor (VEGFR) Signaling in Angiogenesis: A Crucial Target for Anti- and Pro-Angiogenic Therapies. *Genes Cancer*. 2011;2(12):1097-1105. doi:10.1177/1947601911423031

25. Chen Y, Hu H, Yuan X, Fan X, Zhang C. Advances in Immune Checkpoint Inhibitors for Advanced Hepatocellular Carcinoma. *Front Immunol*. 2022;13:896752. doi:10.3389/fimmu.2022.896752

26. United States Cancer Statistics: Data Visualizations: Cancer Statistics At a Glance, United States (2020). CDC.gov. Accessed June 21, 2023. Available at https://gis.cdc.gov/Cancer/USCS/#/AtAGlance/

27. American Cancer Society. Cancer Facts & Figures 2023. https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/2023-cancer-facts-figures.html

28. Evrard C, Tachon G, Randrian V, Karayan-Tapon L, Tougeron D. Microsatellite Instability: Diagnosis, Heterogeneity, Discordance, and Clinical Impact in Colorectal Cancer. *Cancers (Basel)*. 2019;11(10)doi:10.3390/cancers11101567

29. Morris VK, Kennedy EB, Baxter NN, et al. Treatment of Metastatic Colorectal Cancer: ASCO Guideline. *J Clin Oncol*. 2023;41(3):678-700. doi:10.1200/JCO.22.01690

30. Minhajat R, Harjianti T, Islam IC, Winarta S, Liyadi YN, Bamatraf NP, Amanuddin R. Bevacizumab side effects and adverse clinical complications in colorectal cancer patients: review article. *Annals of Medicine and Surgery*. 2023;85(8)https://journals.lww.com/annals-of-medicine-and-surgery/fulltext/2023/08000/bevacizumab_side_effects_and_adverse_clinical.26.aspx

31. Parisi A, Ghidini M, Giampieri R, et al. Post-induction Strategies in Metastatic Colorectal Cancer Patients Treated With First-Line Anti-EGFR-Based Treatment: A Systematic Review and Meta-Analysis. *Clin Colorectal Cancer*. 2022;21(3):e162-e170. doi:10.1016/j.clcc.2021.12.005

32. Hoang T, Sohn DK, Kim BC, Cha Y, Kim J. Efficacy and Safety of Systemic Treatments Among Colorectal Cancer Patients: A Network Meta-Analysis of Randomized Controlled Trials. *Frontiers in Oncology*. 2022;11https://www.frontiersin.org/articles/10.3389/fonc.2021.756214

33. Thakur A, Chorawala MR, Patel RS. A systemic review and meta-analysis of Aflibercept plus FOLFIRI regimen as a second-line treatment for metastatic colorectal cancer: A PRISMA compliant pooled analysis of randomized controlled trials and single arm studies to assess efficacy and safety. *Critical Reviews in Oncology/Hematology*. 2023;188:104034. doi:https://doi.org/10.1016/j.critrevonc.2023.104034 https://www.sciencedirect.com/science/article/pii/S1040842823001221

34. Di Nardo P, Basile D, Siciliano A, et al. Second-line treatment strategies for RAS wild-type colorectal cancer: A systematic review and Network Meta-analysis (NMA). *Digestive and Liver Disease*. 2023, https://doi.org/10.1016/j.dld.2023.07.013doi:https://doi.org/10.1016/j.dld.2023.07.013 https://www.sciencedirect.com/science/article/pii/S1590865823007661

35. Xu S, Sak A, Erol YB. Network Meta-analysis of First-Line Systemic Treatment for Patients With Metastatic Colorectal Cancer. *Cancer Control*. 2021;28:10732748211033497. doi:10.1177/10732748211033497 Accessed 2023/07/21. Available at https://doi.org/10.1177/10732748211033497

36. Kawai S, Takeshima N, Hayasaka Y, et al. Comparison of irinotecan and oxaliplatin as the first-line therapies for metastatic colorectal cancer: a meta-analysis. *BMC Cancer*. 2021;21(1):116. doi:10.1186/s12885-021-07823-7 https://doi.org/10.1186/s12885-021-07823-7

37. Wu C-C, Hsu C-W, Hsieh M-C, Wang J-H, Chang M-C, Yang C-S, Su Y-C. Optimal Sequence and Second-Line Systemic Treatment of Patients with RAS Wild-Type Metastatic Colorectal Cancer: A Meta-Analysis. *Journal of Clinical Medicine*. 2021;10(21)doi:10.3390/jcm10215166

38. Xu Z, Peng X, Kong Y, Cui Y, Li Y, Guo Y. The best strategy for metastatic colorectal cancer (mCRC) patients in second-line treatment: A network meta-analysis. *Cancer Treatment and Research Communications*. 2021;29:100455. doi:https://doi.org/10.1016/j.ctarc.2021.100455 https://www.sciencedirect.com/science/article/pii/S2468294221001520

39. Benson A, D'Angelica M, Abrams T, Abbott D, Ahmed A, Anaya D, Anders R. NCCN Guidelines Version 2.2023 Hepatocellular Carcinoma. *NCCN Clinical Practice Guidelines in Oncology*. 2023,

40. Llovet JM, Kelley RK, Villanueva A, et al. Hepatocellular carcinoma. *Nature Reviews Disease Primers*. 2021;7(1):6. doi:10.1038/s41572-020-00240-3 https://doi.org/10.1038/s41572-020-00240-3

41. Bruix J, Qin S, Merle P, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2017;389(10064):56-66. doi:10.1016/s0140-6736(16)32453-9

42. Meyers BM, Knox JJ, Liu DM, McLeod D, Ramjeesingh R, Tam VC, Lim HJ. The evolution of immune checkpoint inhibitor combinations in advanced hepatocellular carcinoma - A systematic review. *Cancer Treat Rev*. 2023;118:102584. doi:10.1016/j.ctrv.2023.102584

43. Li L, Liu HT, Teng YX, et al. Second-line treatment options for hepatocellular carcinoma: current state and challenges for the future. *Expert Opin Investig Drugs*. 2022;31(11):1151-1167. doi:10.1080/13543784.2022.2151891

44. Ben Mousa A. Sorafenib in the treatment of advanced hepatocellular carcinoma. *Saudi J Gastroenterol*. 2008;14(1):40-42. doi:10.4103/1319-3767.37808

45. Cheng AL, Qin S, Ikeda M, et al. Updated efficacy and safety data from IMbrave150: Atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. *J Hepatol*. 2022;76(4):862-873. doi:10.1016/j.jhep.2021.11.030

46. Zhu AX, Park JO, Ryoo BY, et al. Ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib (REACH): a randomised, double-blind, multicentre, phase 3 trial. *Lancet Oncol*. 2015;16(7):859-870. doi:10.1016/s1470-2045(15)00050-9

47. Su GL, Altayar O, O'Shea R, et al. AGA Clinical Practice Guideline on Systemic Therapy for Hepatocellular Carcinoma. *Gastroenterology*. 2022;162(3):920-934. doi:10.1053/j.gastro.2021.12.276

48. Gordan JD, Kennedy EB, Abou-Alfa GK, et al. Systemic Therapy for Advanced Hepatocellular Carcinoma: ASCO Guideline. *J Clin Oncol*. 2020;38(36):4317-4345. doi:10.1200/jco.20.02672

49. Fong KY, Zhao JJ, Sultana R, et al. First-Line Systemic Therapies for Advanced Hepatocellular Carcinoma: A Systematic Review and Patient-Level Network Meta-Analysis. *Liver Cancer*. 2023;12(1):7-18. doi:10.1159/000526639

50. Fulgenzi CAM, Scheiner B, Korolewicz J, et al. Efficacy and safety of frontline systemic therapy for advanced HCC: A network meta-analysis of landmark phase III trials. *JHEP Rep*. 2023;5(5):100702. doi:10.1016/j.jhepr.2023.100702

51. Lei Q, Yan X, Zou H, Jiang Y, Lai Y, Ung COL, Hu H. Efficacy and safety of monotherapy and combination therapy of immune checkpoint inhibitors as first-line treatment for unresectable hepatocellular carcinoma: a systematic review, meta-analysis and network meta-analysis. *Discov Oncol*. 2022;13(1):95. doi:10.1007/s12672-022-00559-1

52. Sun K-X, Cao S-S, Shi F-H, et al. First-line treatments for advanced hepatocellular carcinoma: a network meta-analysis and cost-effectiveness analysis in China and the United States. *Therapeutic Advances in Gastroenterology*. 2022;15:17562848221140662. doi:10.1177/17562848221140662 Accessed 2023/07/11. Available at https://doi.org/10.1177/17562848221140662

53. Kudo M, Montal R, Finn RS, et al. Objective Response Predicts Survival in Advanced Hepatocellular Carcinoma Treated with Systemic Therapies. *Clin Cancer Res*. 2022;28(16):3443-3451. doi:10.1158/1078-0432.Ccr-21-3135

54. Ciliberto D, Caridà G, Staropoli N, et al. First-line systemic treatment for hepatocellular carcinoma: A systematic review and network meta-analysis. *Heliyon*. 2023;9(8)doi:10.1016/j.heliyon.2023.e18696 Accessed 2023/08/30. Available at https://doi.org/10.1016/j.heliyon.2023.e18696

55. Solimando AG, Susca N, Argentiero A, et al. Second-line treatments for Advanced Hepatocellular Carcinoma: A Systematic Review and Bayesian Network Meta-analysis. *Clin Exp Med*. 2022;22(1):65-74. doi:10.1007/s10238-021-00727-7

56. Sonbol MB, Riaz IB, Naqvi SAA, et al. Systemic Therapy and Sequencing Options in Advanced Hepatocellular Carcinoma: A Systematic Review and Network Meta-analysis. *JAMA Oncol*. 2020;6(12):e204930. doi:10.1001/jamaoncol.2020.4930

57. Fulgenzi CAM, D'Alessio A, Airoldi C, et al. Comparative efficacy of novel combination strategies for unresectable hepatocellular carcinoma: A network metanalysis of phase III trials. *Eur J Cancer*. 2022;174:57-67. doi:10.1016/j.ejca.2022.06.058

58. Duarte FA, Ferreira CG, Dienstmann R, et al. Barriers in precision medicine implementation among Advanced Nonsquamous Cell Lung Cancer-patients: A Real-World Evidence Scenario. *J Mark Access Health Policy*. 2022;10(1):2077905. doi:10.1080/20016689.2022.2077905

59. Singh N, Jaiyesimi IA, Ismaila N, Leighl NB, Mamdani H, Phillips T, Owen DH. Therapy for Stage IV Non–Small-Cell Lung Cancer Without Driver Alterations: ASCO Living Guideline, Version 2023.1. *Journal of Clinical Oncology*. 2023;41(15):e51-e62. doi:10.1200/JCO.23.00282 Accessed 2023/07/27. Available at https://doi.org/10.1200/JCO.23.00282

60. Singh N, Temin S, Baker S, et al. Therapy for Stage IV Non–Small-Cell Lung Cancer With Driver Alterations: ASCO Living Guideline. *Journal of Clinical Oncology*. 2022;40(28):3310-3322. doi:10.1200/JCO.22.00824 Accessed 2023/07/27. Available at https://doi.org/10.1200/JCO.22.00824

61. Liu T, Wu S, Fang W, et al. Identifying optimal first-line immune checkpoint inhibitors based regiments for advanced non-small cell lung cancer without oncogenic driver mutations: A systematic review and network meta-analysis. *PLoS One*. 2023;18(4):e0283719. doi:10.1371/journal.pone.0283719

62. Shao T, Zhao M, Liang L, Tang W. A systematic review and network meta-analysis of first-line immune checkpoint inhibitor combination therapies in patients with advanced non-squamous non-small cell lung cancer. *Front Immunol*. 2022;13:948597. doi:10.3389/fimmu.2022.948597

63. Zhang X, Xu Q, Yu X, et al. What Is Long-Term Survival and Which First-Line Immunotherapy Brings Long-Term Survival for Advanced Wild-Type Non-Small Cell Lung Cancer: A Network Meta-Analysis Based on Integrated Analysis. *Front Immunol*. 2022;13:764643. doi:10.3389/fimmu.2022.764643

64. Yin Q, Dai L, Sun R, Ke P, Liu L, Jiang B. Clinical Efficacy of Immune Checkpoint Inhibitors in Non-Small Cell Lung Cancer Patients with Liver Metastases: A Network Meta-Analysis of Nine Randomized Controlled Trials. *Cancer Res Treat*. 2022;54(3):803-816. doi:10.4143/crt.2021.764

65. Haeussler K, Wang X, Winfree KB, et al. Efficacy and safety of first-line therapies in EGFR-mutated advanced non-small-cell lung cancer: a network meta-analysis. *Future Oncol*. 2022;18(16):2007-2028. doi:10.2217/fon-2021-0885

66. Chen C, Zhang C, Lin H, Liu Q, Wu L, Zhou C, Zhang J. First-line therapeutic strategy for patients with advanced non-small cell lung cancer with Leu858Arg epidermal growth factor receptor mutations: a Bayesian network meta-analysis. *Ther Adv Chronic Dis*. 2022;13:20406223221125706. doi:10.1177/20406223221125706

67. Zhao Y, Liu J, Cai X, et al. Efficacy and safety of first line treatments for patients with advanced epidermal growth factor receptor mutated, non-small cell lung cancer: systematic review and network meta-analysis. *BMJ*. 2019;367:l5460. doi:10.1136/bmj.l5460

68. Chan SK, Choi HC, Lee VH. Overall Survival Benefits of First-Line Treatments for Asian Patients with Advanced Epidermal Growth Factor Receptor-Mutated NSCLC Harboring Exon 19 Deletion: A Systematic Review and Network Meta-Analysis. *Cancers (Basel)*. 2022;14(14)doi:10.3390/cancers14143362

69. Chan S-K, Choi HC-W, Lee VH-F. Overall Survival Benefits of First-Line Treatments for Asian Patients With Advanced EGFR-Mutated NSCLC Harboring L858R Mutation: A Systematic Review and Network Meta-Analysis. *JTO Clin Res Rep*. 2022;3(5):100322-100322. doi:10.1016/j.jtocrr.2022.100322

70. Li J, Chen Y, Hu F, et al. Comparison of the efficacy and safety in the treatment strategies between chemotherapy combined with antiangiogenic and with immune checkpoint inhibitors in advanced non-small cell lung cancer patients with negative PD-L1 expression: A network meta-analysis. *Front Oncol*. 2022;12:1001503. doi:10.3389/fonc.2022.1001503

71. Kim JH, Jeong SY, Lee JJ, Park ST, Kim HS. A Bayesian Network Meta-Analysis of First-Line Treatments for Non-Small Cell Lung Cancer with High Programmed Death Ligand-1 Expression. *J Clin Med*. 2022;11(6)doi:10.3390/jcm11061492

72. Chai Y, Wu X, Bai H, Duan J. Combined Immunotherapy with Chemotherapy versus Bevacizumab with Chemotherapy in First-Line Treatment of Driver-Gene-Negative Non-Squamous Non-Small Cell Lung Cancer: An Updated Systematic Review and Network Meta-Analysis. *J Clin Med*. 2022;11(6)doi:10.3390/jcm11061655

73. Tamimi A, Juweid M. Chapter 8. Epidemiology and Outcome of Glioblastoma. In: De Vleeschouwer S, ed. *Glioblastoma [Internet]*. Codon Publications; 2017:chap Chapter 8. Available at https://www.ncbi.nlm.nih.gov/books/NBK470003/

74. Louis D, Schiff D, Batchelor T. Classification and pathologic diagnosis of gliomas, glioneuronal tumors, and neuronal tumors. UptoDate; 2022. Last Updated August 19, 2022.

75. Batchelor T. Initial treatment and prognosis of IDH-wildtype glioblastoma in adults. UptoDate; 2022. Last Updated May 24, 2023.

76. Mohile NA, Messersmith H, Gatson NT, et al. Therapy for Diffuse Astrocytic and Oligodendroglial Tumors in Adults: ASCO-SNO Guideline. *J Clin Oncol*. 2022;40(4):403-426. doi:10.1200/jco.21.02036

77. Abu-Rustum N, Yashar C, Arend R, et al. NCCN Guidelines Version 1.2023 Cervical Cancer. *NCCN Clinical Practice Guidelines in Oncology*. 2023,

78. Chen L-m, Berek J. Overview of epithelial carcinoma of the ovary, fallopian tube, and peritoneum. Goff B, Dizon D; 2023. Last Updated May 2023.

79. Berek JS, Renz M, Kehoe S, Kumar L, Friedlander M. Cancer of the ovary, fallopian tube, and peritoneum: 2021 update. *Int J Gynaecol Obstet*. 2021;155 Suppl 1(Suppl 1):61-85. doi:10.1002/ijgo.13878

80. Jaffer Ajani, D'Amico T, Bentrem D, et al. NCCN Guidelines: Gastric Cancer, Version, 1.2023 *National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®)*. https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf

81. Jaffer Ajani, D'Amico T, Bentrem D, et al. NCCN Guidelines: Esophageal and Esophagogastric Junction Cancers, Version 3.2023 *National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®)*. https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf

82. Shah MA, Kennedy EB, Alarcon-Rozas AE, et al. Immunotherapy and Targeted Therapy for Advanced Gastroesophageal Cancer: ASCO Guideline. *Journal of Clinical Oncology*. 2023;41(7):1470-1491. doi:10.1200/JCO.22.02331 Accessed 2023/07/30. Available at https://doi.org/10.1200/JCO.22.02331

83. He YM, Yu C, Li WB, Li ZP, Xu N. Evaluation of short-term effectiveness of eight targeted agents combined with chemotherapy for treating esophageal-gastric junction adenocarcinoma: A network meta-analysis. *J Cell Biochem*. 2018;119(1):1183-1192. doi:10.1002/jcb.26288

84. de Back T, Nijskens I, Schafrat P, Chalabi M, Kazemier G, Vermeulen L, Sommeijer D. Evaluation of Systemic Treatments of Small Intestinal Adenocarcinomas: A Systematic Review and Meta-analysis. *JAMA Network Open*. 2023;6(2):e230631-e230631. doi:10.1001/jamanetworkopen.2023.0631 Accessed 7/11/2023. Available at https://doi.org/10.1001/jamanetworkopen.2023.0631

85. Di Nardo P, Garattini SK, Torrisi E, Fanotto V, Miolo G, Buonadonna A, Puglisi F. Systemic Treatments for Advanced Small Bowel Adenocarcinoma: A Systematic Review. *Cancers (Basel)*. 2022;14(6)doi:10.3390/cancers14061502

86. Benson A, Venook A, Pendersen K, Al-Hawary M, Azad N, Chen Y-J, Ciombor K. NCCN Guidelines: Small Bowel Adenocarcinoma, Version 1.2023 *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)*.

87. US Food and Drug Administration. Review and Approval. FDA.gov. 2022. Last Updated December 2022. Accessed September 13, 2023. Available at https://www.fda.gov/drugs/biosimilars/review-and-approval#:~:text=A%20biosimilar%20is%20a%20biologic,biologic%2C%20called%20a%20reference%20product.

88. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi:10.1136/bmj.n71

89. CABOMETYX (cabozantinib) tablets, for oral use. Package Insert. Exelixis Inc.; July 2022.

90. FOTIVDA (tivozanib) capsules, for oral use. Package Insert. Catalent CTS; March 2021.

91. INLYTA (axitinib) tablets, for oral administration. Package Insert. Pfizer Laboratories; September 2022.

92. LENVIMA (lenvatinib) capsules, for oral use. Package Insert. Eisai Inc.; November 2022.

93. NEXAVAR (sorafenib) tablets, for oral use. Package Insert. Bayer HealthCare Pharmaceuticals Inc.; July 2020.

94. SUTENT (sunitinib malate) capsules, for oral use. Package Insert. Pfizer Laboratories; August 2021.

95. VOTRIENT (pazopanib) tablets, for oral use. Package Insert. Novartis Pharmaceuticals Corporation; December 2021.

96. CAPRELSA (vandetanib) tablets, for oral use. Package Insert. Corporation G; December 2022.

97. COMETRIQ (cabozantinib) capsules, for oral use Package Insert. Exelixis Inc.; August 2023.

98. STIVARGA (regorafenib) tablets, for oral use. Package Insert. Bayer HealthCare Pharmaceuticals Inc.; December 2020.

# APPENDIX A - PRODUCT INDICATIONS AND DOSING

*Table A1. Intravenous Anti-VEGF Indications and Dosing[a, 1-7]*

| Bevacizumab and Biosimilars[b] |
|---|
| **Colorectal Cancer (metastatic)**<br>• 5 or 10 mg/kg every 2 weeks combined with IV fluorouracil-based chemotherapy for first- or second-line treatment<br>• 5 mg/ kg every 2 weeks or 7.5 mg/kg every 3 weeks combined with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy for second-line treatment in patients who have progressed on a first-line bevacizumab regimen |
| **Non-squamous Non-small Cell Lung cancer** (unresectable, locally advanced, recurrent or metastatic)<br>• 15 mg/kg every 3 weeks with carboplatin and paclitaxel for first-line treatment |
| **Glioblastoma (recurrent) in adults**<br>• 10 mg/kg every 2 weeks |
| **Renal cell carcinoma (metastatic)**<br>• 10 mg/kg every 2 weeks with interferon alfa |
| **Cervical cancer (persistent, recurrent, or metastatic)**<br>• 15 mg/kg every 3 weeks with paclitaxel and cisplatin, or paclitaxel and topotecan |
| **Epithelial ovarian, fallopian tube, or primary peritoneal cancer**<br>• For platinum-resistant recurrent disease treated with no more than 2 prior chemotherapy regimens: 10 mg/kg every 2 weeks with paclitaxel, pegylated liposomal doxorubicin, or topotecan given every week; or 15 mg/kg every 3 weeks with topotecan given every 3 weeks<br>• For stage III or IV disease following initial surgical resection[c]: 15 mg/kg every 3 weeks with carboplatin and paclitaxel for up to 6 cycles, followed by 15 mg/kg every 3 weeks as a single agent, for a total of up to 22 cycles<br>• For platinum-sensitive recurrent disease[c]: 15 mg/kg every 3 weeks with carboplatin and paclitaxel for 6-8 cycles, followed by 15 mg/kg every 3 weeks as a single agent; or 15 mg/kg every 3 weeks with carboplatin and gemcitabine for 6-10 cycles, followed by 15 mg/kg every 3 weeks as a single agent |
| **Hepatocellular carcinoma**[d] (HCC)<br>• For the treatment of patients with unresectable or metastatic HCC who have not received prior systemic therapy: 15 mg/kg after administration of 1,200mg of atezolizumab every 3 weeks |

[a] *See full prescribing information for dosage modifications in the event of adverse reactions*

[b] *Biosimilars do not have the full set of approved indications as the originator Avastin; refer further notes for which biosimilars do not have a particular indication*

[c] *The biosimilar Alymsys (bevacizumab-maly) is not FDA-approved for this indication according its package insert, last updated in 2022*

[d] *No biosimilar of Avastin is indicated for hepatocellular carcinoma*

[e] *In cases with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations, disease progression is considered as treatment failure with an FDA-approved therapy for the respective aberration*

*Table A1. Intravenous Anti-VEGF Indications and Dosing[a, 1-7]*

| Ramucirumab |
|---|
| **Colorectal Cancer (metastatic),** with disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine<br>• 8 mg/kg every 2 weeks prior to fluorouracil, leucovorin, and irinotecan (FOLFIRI)<br>**Non-Small Cell Lung Cancer (metastatic):**<br>• For first-line treatment for tumors with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations.<br>  ○ 10 mg/kg every 2 weeks with daily erlotinib<br>• For disease progression on or after platinum-based chemotherapy[e]<br>  ○ 10 mg/kg on Day 1 of a 21-day cycle prior to docetaxel<br>**Hepatocellular Carcinoma,** in patients with an alpha fetoprotein (AFP) of ≥400 ng/mL and have been treated with sorafenib<br>• 8 mg/kg every 2 weeks<br>**Gastric or gastro-esophageal junction (GEJ) adenocarcinoma (advanced or metastatic)** with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy:<br>• 8 mg/kg every 2 weeks as a single agent or in combination (ie, administered prior to) with weekly paclitaxel |
| **Ziv-aflibercept** |
| **Colorectal Cancer (metastatic)** that is resistant to or has progressed following an oxaliplatin-containing regimen<br>• 4 mg/kg as an intravenous infusion over 1 hour every 2 weeks, in combination with fluorouracil, leucovorin, irinotecan (FOLFIRI) |

*[a] See full prescribing information for dosage modifications in the event of adverse reactions*

*[b] Biosimilars do not have the full set of approved indications as the originator Avastin; refer further notes for which biosimilars do not have a particular indication*

*[c] The biosimilar Alymsys (bevacizumab-maly) is not FDA-approved for this indication according its package insert, last updated in 2022*

*[d] No biosimilar of Avastin is indicated for hepatocellular carcinoma*

*[e] In cases with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations, disease progression is considered as treatment failure with an FDA-approved therapy for the respective aberration*

# APPENDIX B - LITERATURE SEARCH

The phased literature search approach involved screening the most recently published SRs first, then refining the search to later publication years tailored to certain drugs/indications as needed (per the rationale described in **Table B1**). The search strategies for each literature search (A-D in Box 1) are included in following subsections after the table.

*Table B1. Phased Literature Search Approach for Head-to-head SRs/RCTs*

A. *SR Search in Ovid-Medline*
   a. Searched for all IV anti-VEGF drugs and the 3 overlapping indications, in SRs published within the last year.
      i. Identified a 2023 SR showing no head-to-head studies with ziv-aflibercet vs. bevacizumab or ramucirumab for metastatic colorectal cancer (mCRC).[33] Ziv-aflibercept (which is approved only for mCRC) was removed from further SR searches of older publication years.
   b. Searched for bevacizumab or ramucirumab and overlapping indications from 2022 onward.
      i. Found many SRs showing no head-to-head studies of bevacizumab and ramucirumab for hepatocellular carcinoma (HCC) or mCRC (1 of these SRs also showed no IV anti-VEGF head-to-head comparison with ziv-aflibercept for mCRC).
      ii. With respect to HCC, we would not expect bevacizumab and ramucirumab to be compared since one is used for first-line and the other is used for subsequent therapy (consistent with FDA approvals and guideline recommendations). The absence of head-to-head studies in the identified SRs also support this notion.
      iii. Regarding non-small cell lung cancer (NSCLC), several SRs were identified that show no head-to-head studies between bevacizumab and ramucirumab.

B. *Supplemental SR search in Epistemonikos (2021 onward)*
   a. Searched for bevacizumab or ramucirumab for the treatment of mCRC or NSCLC from 2021 onward. Identified additional SRs from 2021 also showing no head-to-head trials between the reviewed IV anti-VEGF therapies.

C. *Supplemental RCT search in Ovid-Medline*
   a. Searched for bevacizumab vs. ramucirumab comparisons without date restriction

D. *Supplemental RCT search in Embase*
   a. Searched for bevacizumab vs. ramucirumab comparisons for 2021 onward
   b. Searched for aflibercept comparisons for 2022 onward to supplement the SR[33] search

## *A. Ovid-Medline Systematic Review Searches*

*Initial Search*

| Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to November 3, 2023 | | |
|---|---|---|
| **#** | **Searches** | **Results** |
| 1 | exp Colorectal Neoplasms/ or Carcinoma, Non-Small-Cell Lung/ or exp liver neoplasms/ or exp adenoma, liver cell/ or exp carcinoma, hepatocellular/ | 488732 |
| 2 | (colorectal or colon or hepatocellular or liver or non-small-cell-lung).ti,ab. | 1384593 |
| **3** | (bevacizumab or ramucirumab or aflibercept or zivaflibercept).ti,ab,kw,kf. | 23651 |
| 4 | meta-analysis/ or (metaanaly$ or meta-analy$).ti,ab,kw,kf. or "Systematic Review"/ or ((systematic* adj3 review*) or (systematic* adj2 search*) or cochrane$ or (overview adj4 review)).ti,ab,kw,kf. or (cochrane$ or systematic review?).jw. | 547381 |
| 5 | (Medline or Embase or Pubmed or literature-search).ab. or (systematic-review or meta-analysis).pt. | 505999 |
| **6** | 4 or 5 (SR filter) | 649142 |
| **7** | 1 or 2 (Overlapping FDA Indicated Disease States) | 1509533 |
| 8 | 3 and 6 and 7 (SR result pool) | 503 |
| 9 | limit 8 to yr="**2023** -Current" (SR result pool (2023) for BEV, RAM and ZIV) | 43 |
| **10** | (bevacizumab or ramucirumab).ti,ab,kw,kf. | 21353 |
| 11 | 6 and 7 and 10 | 490 |
| 12 | limit 11 to yr="**2022** -Current" (SR result pool (2022 onward) for BEV and RAM) | 95 |
| 13 | 9 or 12 | **105** |

Updated Search to January 8, 2024: Added 7 additional results compared to prior search

| Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to January 08, 2024 | | |
|---|---|---|
| **#** | **Searches** | **Results** |
| 1 | exp Colorectal Neoplasms/ or Carcinoma, Non-Small-Cell Lung/ or exp liver neoplasms/ or exp adenoma, liver cell/ or exp carcinoma, hepatocellular/ | 493090 |
| 2 | (colorectal or colon or hepatocellular or liver or non-small-cell-lung).ti,ab. | 1396924 |
| 3 | (bevacizumab or ramucirumab or aflibercept or zivaflibercept).ti,ab,kw,kf. or Bevacizumab/ | 26424 |
| 4 | meta-analysis/ or (metaanaly$ or meta-analy$).ti,ab,kw,kf. or "Systematic Review"/ or ((systematic* adj3 review*) or (systematic* adj2 search*) or cochrane$ or (overview adj4 review)).ti,ab,kw,kf. or (cochrane$ or systematic review?).jw. | 558547 |
| 5 | (Medline or Embase or Pubmed or literature-search).ab. or (systematic-review or meta-analysis).pt. | 516594 |
| 6 | 4 or 5 (SR filter) | 662009 |
| 7 | 1 or 2 (Overlapping FDA Indicated Disease States) | 1522507 |
| 8 | 3 and 6 and 7 | 520 |
| 9 | limit 8 to yr="**2023 -Current**" | 50 |

## *B.* Epistemonikos Systematic Reviews Search

- title:(colorectal OR colon OR non-small-cell-lung) OR abstract:(colorectal OR colon OR non-small-cell-lung)) AND (title:(bevacizumab OR ramucirumab) OR abstract:(bevacizumab OR ramucirumab))
    - Results limited from 2021 onward (November 3, 2023): 38
    - Results limited from 2021 onward (January 9, 2024 update): 39

### C. *Ovid-Medline Supplemental RCT Search*

*Initial Search: RCTs: all years, bevacizumab AND ramucirumab*

| Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to November 3, 2023 | | |
|---|---|---|
| # | **Searches** | **Results** |
| 1 | (bevacizumab and ramucirumab).ti,ab,kw,kf. | 294 |
| 2 | ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (exp animals/ not humans.sh.) | 1434383 |
| 3 | 1 and 2 | **78** |

*Updated search to January 08, 2024*: Added 1 additional result compared to prior search

| Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to January 08, 2024 | | |
|---|---|---|
| # | **Searches** | **Results** |
| 1 | (bevacizumab and ramucirumab).ti,ab,kw,kf. | 296 |
| 2 | ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (exp animals/ not humans.sh.) | 1446813 |
| 3 | 1 and 2 | **79** |

### D. *Embase Supplemental RCT Search*

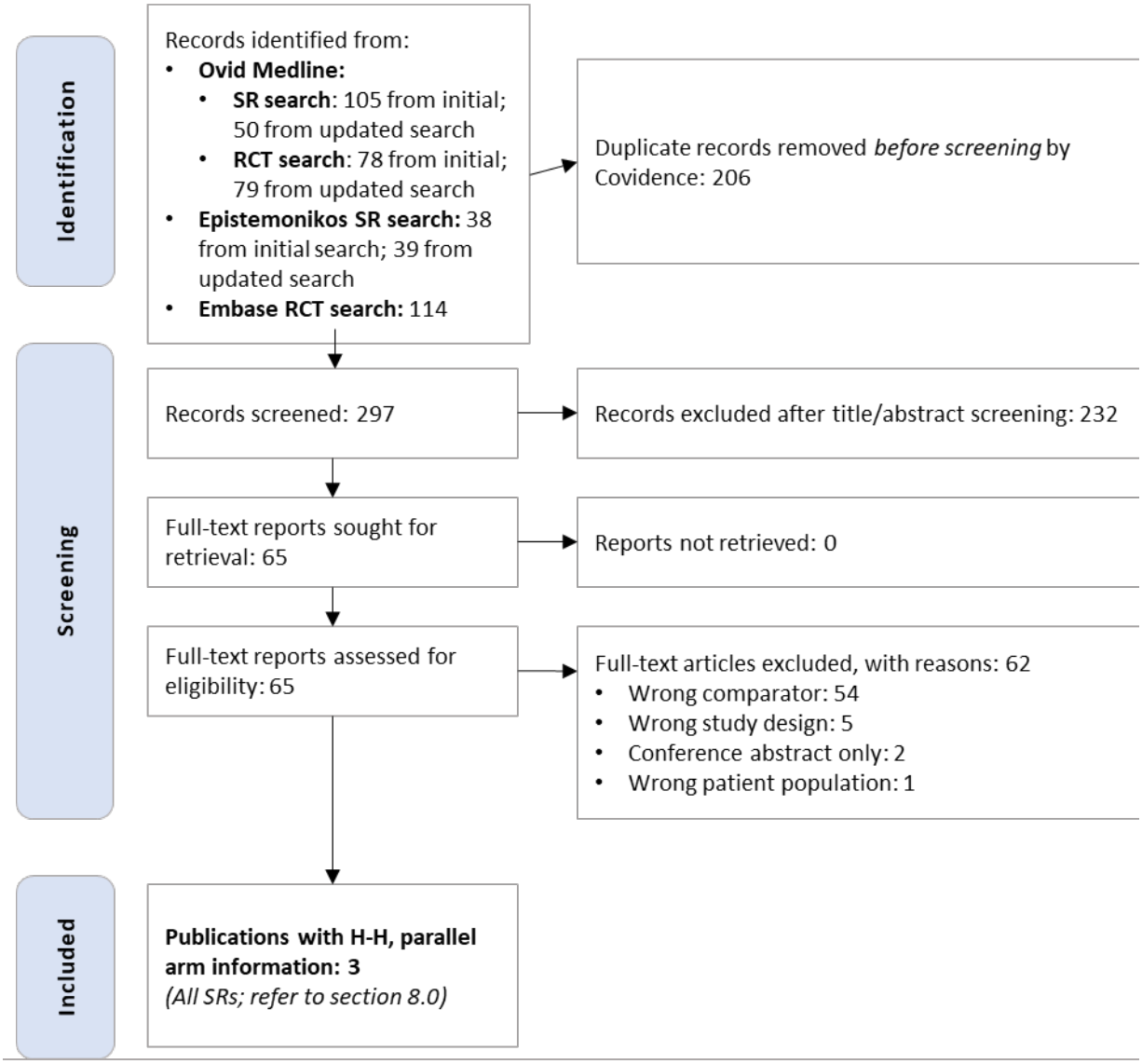
*RCT Search: bevacizumab AND ramucirumab (2021 onward), or aflibercept comparisons (2022 onward)*

| Embase query executed November 3, 2023 | | |
|---|---|---|
| **No.** | | **Results** |
| #8 | #4 OR #7 | **114** |
| #7 | #6 AND (2022:py OR 2023:py) | 68 |
| #6 | #2 AND #5 | 508 |
| #5 | aflibercept:ti,ab,kw AND (bevacizumab:ti,ab,kw OR ramucirumab:ti,ab,kw) | 1846 |
| #4 | #3 AND (2021:py OR 2022:py OR 2023:py) | 52 |
| #3 | #1 AND #2 | 198 |

| Embase query executed November 3, 2023 | | |
|---|---|---|
| **No.** | | **Results** |
| #2 | ('crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR random*:de,ab,ti OR factorial*:de,ab,ti OR crossover*:de,ab,ti OR ((cross NEXT/1 over*):de,ab,ti) OR placebo*:de,ab,ti OR ((doubl* NEAR/1 blind*):de,ab,ti) OR ((singl* NEAR/1 blind*):de,ab,ti) OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti) AND [english]/lim | 3025888 |
| #1 | bevacizumab:ti,ab,kw AND ramucirumab:ti,ab,kw | 464 |

# APPENDIX C- PUBLICATION SCREENING

*Appendix C, Figure 1. PRISMA Flow Chart[a] for Publication Screening*




*Abbreviations: H-H, head to head; RCT, randomized controlled trial; SR, systematic review*

*[a] Modified from Page et al. 2021[88]*

# APPENDIX D: EXCLUDED STUIDES

### Wrong Comparator

Chai Y, Wu X, Bai H, Duan J. Combined Immunotherapy with Chemotherapy versus Bevacizumab with Chemotherapy in First-Line Treatment of Driver-Gene-Negative Non-Squamous Non-Small Cell Lung Cancer: An Updated Systematic Review and Network Meta-Analysis. Journal of clinical medicine. 2022;11(6)doi:https://dx.doi.org/10.3390/jcm11061655

Chan S-K, Choi HC-W, Lee VH-F. Overall Survival Benefits of First-Line Treatments for Asian Patients with Advanced Epidermal Growth Factor Receptor-Mutated NSCLC Harboring Exon 19 Deletion: A Systematic Review and Network Meta-Analysis. Cancers. 2022;14(14)doi:https://dx.doi.org/10.3390/cancers14143362

Chan S-K, Choi HC-W, Lee VH-F. Overall Survival Benefits of First-Line Treatments for Asian Patients With Advanced EGFR-Mutated NSCLC Harboring L858R Mutation: A Systematic Review and Network Meta-Analysis. JTO clinical and research reports. 2022;3(5):100322. doi:https://dx.doi.org/10.1016/j.jtocrr.2022.100322

Chen C, Zhang C, Lin H, et al. First-line therapeutic strategy for patients with advanced non-small cell lung cancer with Leu858Arg epidermal growth factor receptor mutations: a Bayesian network meta-analysis. Therapeutic advances in chronic disease. 2022;13(101532140):20406223221125706. doi:https://dx.doi.org/10.1177/20406223221125706

Chen W, Miao J, Wang Y, Xing W, Xu X, Wu R. Comparison of the efficacy and safety of first-line treatments for of advanced EGFR mutation-positive non-small-cell lung cancer in Asian populations: a systematic review and network meta-analysis. Frontiers in pharmacology. 2023;14(101548923):1212313. doi:https://dx.doi.org/10.3389/fphar.2023.1212313

Chen Z, Jiang S, Li X, et al. Efficacy and safety of anti-angiogenic drugs combined with erlotinib in the treatment of advanced non-small cell lung cancer: a meta-analysis of randomized clinical trials. Annals of palliative medicine. 2021;10(3):2687-2698. doi:https://dx.doi.org/10.21037/apm-20-1621

Ciliberto D, Carida G, Staropoli N, et al. First-line systemic treatment for hepatocellular carcinoma: A systematic review and network meta-analysis. Heliyon. 2023;9(8):e18696. doi:https://dx.doi.org/10.1016/j.heliyon.2023.e18696

Di Nardo P, Basile D, Siciliano A, et al. Second-line treatment strategies for RAS wild-type colorectal cancer: A systematic review and Network Meta-analysis (NMA). Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver. 2023;(dqk, 100958385)doi:https://dx.doi.org/10.1016/j.dld.2023.07.013

Du S, Cao K, Wang Z, Lin D. Clinical efficacy and safety of atezolizumab plus bevacizumab versus lenvatinib in the treatment of advanced hepatocellular carcinoma: A systematic review and meta-analysis. Medicine. 2023;102(23):e33852. doi:https://dx.doi.org/10.1097/MD.0000000000033852

Ergün Y, Uçar G, Açıkgöz Y, et al. 1226P Efficacy and safety of Anti-EGFR TKIs combined with bevacizumab or ramucirumab in the first-line treatment of non-small cell lung cancer: Meta-analysis of randomized controlled trials. Annals of Oncology. 2021;32((Ergün Y.) Medical Oncology, Batman Training and Research Hospital, Batman, Turkey(Uçar G.; Açıkgöz Y.; Dirikoç M.; Esen S.A.; Bardakçı M.; Uncu D.) Medical Oncology, Ankara City Hospital, Ankara, Turkey):S972-S973. doi:10.1016/j.annonc.2021.08.1831

Fedyanin M, Polyanskaya E, Elsnukaeva K, Tryakin A, Pokataev I, Tjulandin S. Is antiangiogenic therapynecessary for patients withmetastatic colorectal cancer(mCRC) and mutation in the BRAF gene? Results of the systematicreview and meta-analysis. Journal of Clinical Oncology. 2021;39(3 SUPPL)doi:10.1200/JCO.2021.39.3_suppl.88

Fong KY, Zhao JJ, Sultana R, et al. First-Line Systemic Therapies for Advanced Hepatocellular Carcinoma: A Systematic Review and Patient-Level Network Meta-Analysis. Liver cancer. 2023;12(1):7-18. doi:https://dx.doi.org/10.1159/000526639

Fulgenzi CAM, D'Alessio A, Airoldi C, et al. Comparative efficacy of novel combination strategies for unresectable hepatocellular carcinoma: A network metanalysis of phase III trials. European journal of cancer (Oxford, England : 1990). 2022;174(arv, 9005373):57-67. doi:https://dx.doi.org/10.1016/j.ejca.2022.06.058

Fulgenzi CAM, Scheiner B, Korolewicz J, et al. Efficacy and safety of frontline systemic therapy for advanced HCC: A network meta-analysis of landmark phase III trials. JHEP reports : innovation in hepatology. 2023;5(5):100702. doi:https://dx.doi.org/10.1016/j.jhepr.2023.100702

Gao L, Tang L, Hu Z, Peng J, Li X, Liu B. Comparison of the efficacy and safety of third-line treatments for metastatic colorectal cancer: a systematic review and network meta-analysis. Front Oncol. 2023 Sep 21;13:1269203. doi: 10.3389/fonc.2023.1269203. PMID: 37810981; PMCID: PMC10552753.

Gordan JD, Kennedy EB, Abou-Alfa GK, et al. Systemic Therapy for Advanced Hepatocellular Carcinoma: ASCO Guideline. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2020;38(36):4317-4345. doi:https://dx.doi.org/10.1200/JCO.20.02672

Haeussler K, Wang X, Winfree KB, et al. Efficacy and safety of first-line therapies in EGFR-mutated advanced non-small-cell lung cancer: a network meta-analysis. Future oncology (London, England). 2022;18(16):2007-2028. doi:https://dx.doi.org/10.2217/fon-2021-0885

He Y-M, Yu C, Li W-B, Li Z-P, Xu N. Evaluation of short-term effectiveness of eight targeted agents combined with chemotherapy for treating esophageal-gastric junction adenocarcinoma: A network meta-analysis. Journal of cellular biochemistry. 2018;119(1):1183-1192. doi:https://dx.doi.org/10.1002/jcb.26288

Hoang T, Sohn DK, Kim BC, Cha Y, Kim J. Efficacy and Safety of Systemic Treatments Among Colorectal Cancer Patients: A Network Meta-Analysis of Randomized Controlled Trials. Frontiers in oncology. 2021;11:756214. doi:10.3389/fonc.2021.756214

Kawai S, Takeshima N, Hayasaka Y, et al. Comparison of irinotecan and oxaliplatin as the first-line therapies for metastatic colorectal cancer: a meta-analysis. BMC cancer. 2021;21(1):116. doi:10.1186/s12885-021-07823-7

Kim JH, Jeong SY, Lee J-J, Park ST, Kim HS. A Bayesian Network Meta-Analysis of First-Line Treatments for Non-Small Cell Lung Cancer with High Programmed Death Ligand-1 Expression. Journal of clinical medicine. 2022;11(6)doi:https://dx.doi.org/10.3390/jcm11061492

Koilakou S, Petrou P. Economic Evaluation of Monoclonal Antibodies in Metastatic Colorectal Cancer: A Systematic Review. Molecular diagnosis & therapy. 2021;25(6):715-734. doi:10.1007/s40291-021-00560-4

Kudo M, Montal R, Finn RS, et al. Objective Response Predicts Survival in Advanced Hepatocellular Carcinoma Treated with Systemic Therapies. Clinical cancer research : an official journal of the American Association for Cancer Research. 2022;28(16):3443-3451. doi:https://dx.doi.org/10.1158/1078-0432.CCR-21-3135

Kulkarni AV, Tevethia H, Kumar K, et al. Effectiveness and safety of atezolizumab-bevacizumab in patients with unresectable hepatocellular carcinoma: a systematic review and meta-analysis. eClinicalMedicine. 2023;63doi:10.1016/j.eclinm.2023.102179 Accessed 2023/11/03. Available at https://doi.org/10.1016/j.eclinm.2023.102179

Lei Q, Yan X, Zou H, et al. Efficacy and safety of monotherapy and combination therapy of immune checkpoint inhibitors as first-line treatment for unresectable hepatocellular carcinoma: a systematic review, meta-analysis and network meta-analysis. Discover Oncology. 2022;13(1):95. doi:https://dx.doi.org/10.1007/s12672-022-00559-1

Li J, Chen Y, Hu F, et al. Comparison of the efficacy and safety in the treatment strategies between chemotherapy combined with antiangiogenic and with immune checkpoint inhibitors in advanced non-small cell lung cancer patients with negative PD-L1 expression: A network meta-analys. Frontiers in oncology. 2022;12(101568867):1001503. doi:https://dx.doi.org/10.3389/fonc.2022.1001503

Li L, Liu H-T, Teng Y-X, et al. Second-line treatment options for hepatocellular carcinoma: current state and challenges for the future. Expert opinion on investigational drugs. 2022;31(11):1151-1167. doi:https://dx.doi.org/10.1080/13543784.2022.2151891

Li L, Yang S, Chen Y, et al. Immune Checkpoint Inhibitors Plus an Anti-VEGF Antibody as the First-Line Treatment for Unresectable Hepatocellular Carcinoma: A Network Meta-Analysis and Cost-Effectiveness Analysis. Frontiers in pharmacology. 2022;13(101548923):891008. doi:https://dx.doi.org/10.3389/fphar.2022.891008

Liu K, Zhu Y, Zhu H. Immunotherapy or targeted therapy as the first-line strategies for unresectable hepatocellular carcinoma: A network meta-analysis and cost-effectiveness analysis. Frontiers in immunology. 2022;13(101560960):1103055. doi:https://dx.doi.org/10.3389/fimmu.2022.1103055

Liu T, Wu S, Fang W, et al. Identifying optimal first-line immune checkpoint inhibitors based regiments for advanced non-small cell lung cancer without oncogenic driver mutations: A systematic review and network meta-analysis. PloS one. 2023;18(4):e0283719. doi:https://dx.doi.org/10.1371/journal.pone.0283719

Meyers BM, Knox JJ, Liu DM, et al. The evolution of immune checkpoint inhibitor combinations in advanced hepatocellular carcinoma - A systematic review. Cancer treatment reviews. 2023;118(cnn, 7502030):102584. doi:https://dx.doi.org/10.1016/j.ctrv.2023.102584

Minhajat R, Harjianti T, Islam IC, et al. Bevacizumab side effects and adverse clinical complications in colorectal cancer patients: review article. Annals of medicine and surgery (2012). 2023;85(8):3931-3937. doi:https://dx.doi.org/10.1097/MS9.0000000000000981

Moriwaki T, Gosho M, Sugaya A, Yamada T, Yamamoto Y, Hyodo I. Optimal Maintenance Strategy for First-Line Oxaliplatin-Containing Therapy with or without Bevacizumab in Patients with Metastatic Colorectal Cancer: A Meta-Analysis. Cancer research and treatment : official journal of Korean Cancer Association. 2021;53(3):703-713. doi:10.4143/crt.2020.805

Parisi A, Ghidini M, Giampieri R, et al. Post-induction Strategies in Metastatic Colorectal Cancer Patients Treated With First-Line Anti-EGFR-Based Treatment: A Systematic Review and Meta-Analysis. Clinical colorectal cancer. 2022;21(3):e162-e170. doi:https://dx.doi.org/10.1016/j.clcc.2021.12.005

Ruff SM, Shannon AH, Beane JD, Pawlik TM. Highlighting novel targets in immunotherapy for liver cancer. Expert review of gastroenterology & hepatology. 2022;16(11-12):1029-1041. doi:https://dx.doi.org/10.1080/17474124.2022.2150841

Shao SC, Hung JH, Lai ECC. CO175 Acute Kidney Injury from Intravitreal Anti–Vascular Endothelial Growth Factor Drugs: A Systematic Review and Meta-Analysis. Value in Health. 2023;26(6):S48. doi:10.1016/j.jval.2023.03.2311

Shao T, Zhao M, Liang L, Tang W. A systematic review and network meta-analysis of first-line immune checkpoint inhibitor combination therapies in patients with advanced non-squamous non-small cell lung cancer. Frontiers in immunology. 2022;13(101560960):948597. doi:https://dx.doi.org/10.3389/fimmu.2022.948597

Solimando AG, Susca N, Argentiero A, et al. Second-line treatments for Advanced Hepatocellular Carcinoma: A Systematic Review and Bayesian Network Meta-analysis. Clinical and experimental medicine. 2022;22(1):65-74. doi:https://dx.doi.org/10.1007/s10238-021-00727-7

Sonbol MB, Riaz IB, Naqvi SAA, et al. Systemic Therapy and Sequencing Options in Advanced Hepatocellular Carcinoma: A Systematic Review and Network Meta-analysis. JAMA oncology. 2020;6(12):e204930. doi:https://dx.doi.org/10.1001/jamaoncol.2020.4930

Sun K-X, Cao S-S, Shi F-H, et al. First-line treatments for advanced hepatocellular carcinoma: a network meta-analysis and cost-effectiveness analysis in China and the United States. Therapeutic advances in gastroenterology. 2022;15(101478893):17562848221140662. doi:https://dx.doi.org/10.1177/17562848221140662

Thakur A, Chorawala MR, Patel RS. A systemic review and meta-analysis of Aflibercept plus FOLFIRI regimen as a second-line treatment for metastatic colorectal cancer: A PRISMA compliant pooled analysis of randomized controlled trials and single arm studies to assess efficacy and safety. Critical reviews in oncology/hematology. 2023;188(ago, 8916049):104034. doi:https://dx.doi.org/10.1016/j.critrevonc.2023.104034

Vogel A, Finn RS, Blanchet Zumofen M-H, et al. Atezolizumab in Combination with Bevacizumab for the Management of Patients with Hepatocellular Carcinoma in the First-Line Setting: Systematic Literature Review and Meta-Analysis. Liver Cancer. 2023;12(6):510-520. doi:10.1159/000533166 Accessed 1/9/2024. Available at https://doi.org/10.1159/000533166

Vorla M, Akbar UA, Sheikh D, et al. Safety and efficacy of anti-VEGF antibodies in the treatment of advanced gastric carcinomas. Journal of Clinical Oncology. 2022;40(16)doi:10.1200/JCO.2022.40.16_suppl.e16005

Wu CC, Hsu CW, Hsieh MC, et al. Optimal Sequence and Second-Line Systemic Treatment of Patients with RAS Wild-Type Metastatic Colorectal Cancer: A Meta-Analysis. Journal of clinical medicine. 2021;10(21)doi:10.3390/jcm10215166

Wu D, Jia B, Jia M, Zhao H, Zhao H, Zhou J. Comparative efficacy and safety of systemic therapy for advanced hepatocellular carcinoma: a systematic review and network meta-analysis. Frontiers in Oncology. 2023;13doi:10.3389/fonc.2023.1274754 https://www.frontiersin.org/articles/10.3389/fonc.2023.1274754

Xiao B, Wang W, Zhang D. Risk of bleeding associated with antiangiogenic monoclonal antibodies bevacizumab and ramucirumab: a meta-analysis of 85 randomized controlled trials. OncoTargets and therapy. 2018;11(101514322):5059-5074. doi:https://dx.doi.org/10.2147/OTT.S166151

Xu S, Sak A, Erol YB. Network Meta-analysis of First-Line Systemic Treatment for Patients With Metastatic Colorectal Cancer. Cancer control : journal of the Moffitt Cancer Center. 2021;28:10732748211033497. doi:10.1177/10732748211033497

Xu Z, Peng X, Kong Y, Cui Y, Li Y, Guo Y. The best strategy for metastatic colorectal cancer (mCRC) patients in second-line treatment: A network meta-analysis. Cancer treatment and research communications. 2021;29:100455. doi:10.1016/j.ctarc.2021.100455

Xue J, Li B, Wang Y, et al. Efficacy and Safety of Epidermal Growth Factor Receptor (EGFR)-Tyrosine Kinase Inhibitor Combination Therapy as First-Line Treatment for Patients with Advanced EGFR-Mutated, Non-Small Cell Lung Cancer: A Systematic Review and Bayesian Network Meta-Analysis. Cancers. 2022;14(19)doi:https://dx.doi.org/10.3390/cancers14194894

Yin Q, Dai L, Sun R, Ke P, Liu L, Jiang B. Clinical Efficacy of Immune Checkpoint Inhibitors in Non-Small Cell Lung Cancer Patients with Liver Metastases: A Network Meta-Analysis of Nine Randomized Controlled Trials. Cancer research and treatment. 2022;54(3):803-816. doi:https://dx.doi.org/10.4143/crt.2021.764

Zhang H, You J, Liu W, Chen D, Zhang S, Wang X. The efficacy and safety of bevacizumab combined with FOLFOX regimen in the treatment of advanced colorectal cancer: A systematic review and meta-analysis. Medicine. 2021;100(30):e26714. doi:10.1097/MD.0000000000026714

Zhang X, Xu Q, Yu X, et al. What Is Long-Term Survival and Which First-Line Immunotherapy Brings Long-Term Survival for Advanced Wild-Type Non-Small Cell Lung Cancer: A Network Meta-Analysis Based on Integrated Analysis. Frontiers in immunology. 2022;13(101560960):764643. doi:https://dx.doi.org/10.3389/fimmu.2022.764643

Zhao T-T, Xu H, Xu H-M, et al. The efficacy and safety of targeted therapy with or without chemotherapy in advanced gastric cancer treatment: a network meta-analysis of well-designed randomized controlled trials. Gastric cancer : official journal of the International Gastric Cancer Association and the Japanese Gastric Cancer Association. 2018;21(3):361-371. doi:https://dx.doi.org/10.1007/s10120-018-0813-2

Zhu Y, Liu C, Xu Z, et al. Front-line therapy for brain metastases and non-brain metastases in advanced epidermal growth factor receptor-mutated non-small cell lung cancer: a network meta-analysis. Chinese medical journal. 2023;(0005256, d3b, 7513795)doi:https://dx.doi.org/10.1097/CM9.0000000000002468

### Wrong Study Design

da Silva LL, Matsas S, Aguiar P, Taveira GMT, Barcelos IF, Lopes GL. EP08.02-042 EGFR-TKI +/- Antiangiogenics for EGFR-mutated Advanced NSCLC. Journal of Thoracic Oncology. 2022;17(9):S416-S417. doi:10.1016/j.jtho.2022.07.724

de Castro G, Stock GT, Harada G, Pereira AAL, Sadeghirad B. EP08.02-059 EGFR Tyrosine Kinase Inhibitors and Combination Strategies in First-line Treatment of Advanced NSCLC: A Network Meta-analysis. Journal of Thoracic Oncology. 2022;17(9):S426-S427. doi:10.1016/j.jtho.2022.07.741

Singh N, Temin S, Baker S, Jr., et al. Therapy for Stage IV Non-Small-Cell Lung Cancer Without Driver Alterations: ASCO Living Guideline. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2022;40(28):3323-3343. doi:https://dx.doi.org/10.1200/JCO.22.00825

Van Leeuwen MT, Luu S, Gurney H, et al. Cardiovascular toxicity of targeted therapies for cancer: An overview of systematic reviews. JNCI Cancer Spectrum. 2021;4(6)doi:10.1093/JNCICS/PKAA076

Xu D, Luo Y, Wang P, et al. Clinical progress of anti-angiogenic targeted therapy and combination therapy for gastric cancer. Frontiers in Oncology. 2023;13((Xu D.; Wang P.; Li J.; Ma L.; Huang J.; Zhang H.; Yang X.; Li L.; Zheng Y.; Yan P., pyyan@must.edu.mo) Faculty of Chinese Medicine, Macau University of Science and Technology, Macao(Luo Y.) School of Second Clinical Medicine, Guangzhou University of Chin)doi:10.3389/fonc.2023.1148131

### Abstract Only

Amonkar M, Frederickson AM, Aksomaityte A, et al. CO110 Systematic Literature Review (SLR) and Meta-Analysis (MA) of Clinical Outcomes for Second-Line and Higher (≥2L) Targeted Therapies for Advanced Colorectal Cancer (aCRC). Value in Health. 2022;25(12):S39-S40. doi:10.1016/j.jval.2022.09.189

Zhou D, Francis K, Dalrymple J, Lord S, Gebski V, Chee C. First-line treatment options for metastatic EGFR mutant lung cancer-an assessment of risk-benefit trade-offs. Asia-Pacific Journal of Clinical Oncology. 2021;17(SUPPL 4):26. doi:10.1111/ajco.13632

### Wrong Patient Population

Di Nardo P, Garattini SK, Torrisi E, et al. Systemic Treatments for Advanced Small Bowel Adenocarcinoma: A Systematic Review. Cancers. 2022;14(6)doi:https://dx.doi.org/10.3390/cancers14061502

## APPENDIX E: ORAL ANTI-VEGF PRODUCTS BY INDICAITED DISEASE STATE

Table E1, lists the oral anti-VEGF therapies available in the US. Across these agents, there are approved 3 disease areas in common with the IV anti-VEGF agents (mCRC, HCC, and RCC). In addition, the oral anti-VEGF therapies altogether have 5 unique indication areas for which the IV agents are not approved (ie, thyroid, gastrointestinal stromal, soft tissue sarcoma, endometrial, and pancreatic neuroendocrine cancer).

*Table E1. Oral Anti-VEGF Products by Indicated Disease State*[89-98]

| Generic (Brand) | Colorectal cancer, metastatic | Endometrial cancer | Gastro-intestinal stromal | Hepatocellular carcinoma, advanced | Pancreatic neuro-endocrine tumors | Renal cell carcinoma, advanced | Soft tissue sarcoma, advanced | Thyroid Cancer |
|---|---|---|---|---|---|---|---|---|
| **Axitinib** (Inlyta) | | | | | | X (for first-line and subsequent treatment) | | |
| **Carbozantinib** (Cometriq, Cabometyx) | | | | X (for cases previously treated with sorafenib) | | X | | X (advanced or metastatic DTC with progression on VEGF therapy and radioactive iodine-refractory or ineligible; also for progressive, metastatic medullary disease) |
| **Lenvatinib** (Lenvima) | | X (advanced disease, pMMR or not MSI-H) | | X (for first-line treatment of unresectable disease) | | X (for first-line and subsequent treatment) | | X (DTC, locally recurrent or metastatic, progressive, radioactive iodine-refractory) |

*Table E1. Oral Anti-VEGF Products by Indicated Disease State*[89-98]

| **Generic** (Brand) | **Colorectal cancer, metastatic** | **Endometrial cancer** | **Gastro-intestinal stromal** | **Hepatocellular carcinoma, advanced** | **Pancreatic neuro-endocrine tumors** | **Renal cell carcinoma, advanced** | **Soft tissue sarcoma, advanced** | **Thyroid Cancer** |
|---|---|---|---|---|---|---|---|---|
| **Pazopanib** (Votrient) | | | | | | X | X (for cases who received prior chemotherapy) | |
| **Regorafenib** (Stivarga) | X (for later-in line therapy) | | X (locally advanced, unresectable, or metastatic disease with prior treatment with imatinib and sunitinib) | X (for cases previously treated with sorafenib) | | | | |
| **Sorafenib** (Nexavar) | | | | X (for unresectable disease) | | X | | X (for locally recurrent or metastatic, progressive, DTC refractory to radioactive iodine) |
| **Sunitinib** (Sutent) *Generic available* | | | X (for cases with progression or intolerance to imatinib) | | X (for progressive, well-differentiated pancreatic neuroendocrine tumors in adults with unresectable locally advanced or metastatic disease | X | | |

*Table E1. Oral Anti-VEGF Products by Indicated Disease State*[89-98]

| **Generic** (Brand) | **Colorectal cancer, metastatic** | **Endometrial cancer** | **Gastro-intestinal stromal** | **Hepatocellular carcinoma, advanced** | **Pancreatic neuro-endocrine tumors** | **Renal cell carcinoma, advanced** | **Soft tissue sarcoma, advanced** | **Thyroid Cancer** |
|---|---|---|---|---|---|---|---|---|
| **Tivozanib** (Fotivda) | | | | | | X (advanced, relapsed or refractory disease following 2 or more systemic therapies) | | |
| **Vandetanib** (Caprelsa) | | | | | | | | X (for locally advanced or metastatic MTC) |

*Abbreviations: DTC, differentiated thyroid cancer; MSI-H, microsatellite instability-high; MTC, medullary thyroid cancer; pMMR, mismatch repair proficient; VEGF, vascular endothelial growth factor*

*Table E2. Approved Disease Areas in Common Between Oral and IV Anti-VEGF Agents*[1-7,89-98]

| Disease and Agent Approved | Indicated Clinical Scenario |
|---|---|
| **Colorectal cancer, metastatic (mCRC)** | |
| Regorafenib (PO) | For patients previously treated with and oxaliplatin/irinotecan/fluoropyrimidine-based regimen, an anti-VEGF therapy, and, if RAS wild-type, an anti-EGFR therapy; used as monotherapy |
| Bevacizumab/ biosimilars (IV) | For first-line or second-line treatment in combination with fluorouracil-based chemotherapy; or for second-line treatment in cases with progression on a first-line bevacizumab regimen, used in combination with fluoropyrimidine/oxaliplatin regimen |
| Ramucirumab (IV) | For patients with disease progression on or after bevacizumab/oxaliplatin/a fluoropyrimidine; used in combination with FOLFIRI |
| Ziv-aflibercept (IV) | For patients with resistance or progression of disease following an oxaliplatin-containing regimen; used in combination with FOLFIRI |
| **Hepatocellular carcinoma (HCC)** | |
| Cabozantinib (PO) | For patients previously treated with sorafenib; used as monotherapy |
| Levatinib (PO) | For first-line treatment of unresectable HCC |
| Regorafenib (PO) | For patients previously treated with sorafenib; used as monotherapy |
| Sorafenib (PO) | For unresectable HCC as monotherapy |
| Bevacizumab, originator only (IV) | For unresectable or metastatic disease in patients who have not had prior systemic therapy; used in combination with atezolizumab |
| Ramucirumab (IV) | For patients with prior sorafenib treatment who also have alpha fetoprotein of ≥400 ng/mL |
| **Renal cell carcinoma (RCC), metastatic** | |
| Axitinib (PO) | • For first-line treatment of advanced RCC; used in combination with avelumab or pembrolizumab<br>• Also for subsequent therapy after failure of 1 prior systemic therapy; used as monotherapy |
| Cabozantinib (PO) | • For first-line treatment of advanced RCC, used in combination with nivolumab<br>• For treatment of advanced RCC, as monotherapy |
| Levatinib (PO) | • For first-line treatment of adults with advanced RCC, in combination pembrolizumab<br>• For adults with advanced RCC following 1 prior anti-angiogenic therapy; used with everolimus |
| Pazopanib (PO) | For adults with advanced RCC, as monotherapy |
| Sorafenib (PO) | For advanced RCC, as monotherapy |
| Sunitinib (PO) | • For adults with advanced RCC, as monotherapy<br>• For adjuvant therapy in adults with high risk of recurrent RCC following nephrectomy |
| Tivozanib (PO) | For relapsed or refractory advanced RCC following 2 or more prior systemic therapies |
| Bevacizumab/ all biosimilars (IV) | For use in combination with interferon alpha |

*Abbreviations: FOLFIR, fluorouracil, leucovorin, irinotecan; HCC, hepatocellular carcinoma; IV, intravenous; PO, oral; RCC, renal cell carcinoma*