COLLEGE OF PHARMACY
UNIVERSITY OF UTAH

L. S. SKAGGS PHARMACY INSTITUTE

UTAH MEDICAID PT REPORT
MAY 2024

ORAL ANTI-VEGF AGENTS FOR APPROVED ONCOLOGIC DISORDERS

Axitinib (INLYTA)
Cabozantinib (COMETRIQ, CABOMETYX)
Fruquintinib (FRUZAQLA)
Lenvatinib (LENVIMA)
Pazopanib (VOTRIENT)
Regorafenib (STIVARGA)
Sorafenib (NEXAVAR)
Sunitinib (STUENT)
Tivozanib (FOTIVDA)
Vandetanib (CAPRELSA)

Report finalized: April 2024
Report presented: May 2024

Drug Regimen Review Center

Valerie Gonzales, PharmD, Clinical Pharmacist
Monet Luloh, PharmD, Clinical Pharmacist
Lauren Heath, PharmD, MS, Clinical Pharmacist
Kristin Knippenberg, MFA, Administrator and Editor
Jacob Crook, MStat, Data Analyst
Joanne LaFleur, PharmD, MSPH, Director and Associate Professor

University of Utah College of Pharmacy, Drug Regimen Review Center

CONTENTS

LIST OF FIGURES

LIST OF TABLES

ABBREVIATIONS

AEs	adverse events
AFP	alfa fetoprotein
AGA	American Gastroenterological Association
ASCO	American Society of Clinical Oncology
ATC	anaplastic thyroid carcinoma
CAPEOX	oxaliplatin + capecitabine
ccRCC	clear cell renal cell carcinoma
CI	confidence interval
CRC	colorectal cancer
dMMR	deficient mismatch repair
DTC	differentiated thyroid carcinoma
EC	endometrial cancer
EGFR	epidermal growth factor receptor
FOLFIRI	leucovorin + fluorouracil + irinotecan
FOLIRINOX	leucovorin + fluorouracil + irinotecan + oxaliplatin
FOLFOX	leucovorin + fluorouracil + oxaliplatin
FDA	US Food and Drug Administration
GIST	gastrointestinal stromal tumor
ICIs	immune checkpoint inhibitors
ICI-mAb	immune checkpoint inhibitor monoclonal antibody
IDH	isocitrate dehydrogenase
IROX	oxaliplatin + irinotecan
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	hazard ratio
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
MTC	medullary thyroid carcinoma
NAFLD	non-alcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis

NCCN	National Comprehensive Cancer Network
nccRCC	non-clear cell renal cell carcinoma
NETs	neuroendocrine tumors
OS	overall survival
PDL	preferred drug list
PD-1	programmed cell death-1
PD-L1	programmed cell death-1 ligand
PFS	progression free survival
pMMR	proficient mismatch repair
pNET	pancreatic neuroendocrine tumor
PRES	posterior reversible encephalopathy syndrome
PVTT	portal vein tumor thrombus
RCC	renal cell carcinoma
RCTs	randomized controlled trials
SDH	succinate dehydrogenase
SRs	systematic reviews
STS	soft tissue sarcoma, advanced
TKIs	tyrosine kinase inhibitors
TSH	thyroid stimulating hormone
VEGFs	vascular endothelial growth factors
WHO	World Health Organization
WT	wild type

EXECUTIVE SUMMARY

Oral vascular endothelial growth factor (VEGF) inhibitors (ie, anti-VEGFs) inhibit extracellular VEGF receptors on endothelial cells (and in most cases, also affect other kinases), ultimately reducing the downstream VEGF-signaling transduction pathway that stimulates angiogenesis and progression of certain cancers. There are 10 oral anti-VEGFs approved in the US: axitinib, cabozantinib, fruquintinib, lenvatinib, pazopanib, regorafenib, sorafenib, sunitinib, tivozanib, and vandetanib. Altogether, oral anti-VEGFs are approved for the treatment of many oncologic disorders: metastatic colorectal cancer (mCRC), endometrial cancer (EC), gastrointestinal stromal tumors (GISTs), hepatocellular carcinoma (HCC), pancreatic neuroendocrine tumors (pNETs), advanced renal cell carcinoma (RCC), advanced soft tissue sarcoma (STS), and differentiated and medullary thyroid cancers (DTC and MTC, respectively). Of these disorders, 5 are among the top 10 cancer groups with the highest cancer-related incidence or death rate in the US (based on data from 2020) [1]:

- **Liver cancer** (of which 72% of cases are HCC) is attributed to the sixth highest cancer-related death rate in the US.
- **Colorectal cancer** is attributed to the fourth highest cancer-related incidence rate in the US.
- **Uterine cancer** (primarily endometrial cancer [EC] cases) and **thyroid cancer** are attributed to the fourth and fifth highest cancer-related incidence rates in US females, respectively.
- **Kidney/renal pelvis cancer** is attributed to the nineth highest cancer-related incidence rate in the overall US population.

Of the oral anti-VEGFs, lenvatinib has the most approved indications (4); cabozantinib, regorafenib, sorafenib, and sunitinib have 3 indications; pazopanib has 2; and axitinib, fruquintinib, tivozanib, and vandetanib have 1 indication. The agents and their indicated disease states are as follows:

- Axitinib (Inlyta): RCC
- Cabozantinib (Cometriq, Cabometyx): HCC, RCC, and thyroid cancer (DTC and MTC)
- Fruquintinib (Fruzaqla): mCRC
- Lenvatinib (Lenvima): EC, HCC, RCC, and thyroid cancer (DTC)
- Pazopanib (Votrient): RCC and STS
- Regorafenib (Stivarga): mCRC, GIST, and HCC
- Sorafenib (Nexavar): HCC, RCC, and thyroid cancer (DTC)
- Sunitinib (Sutent): GIST, pNETs, and RCC
- Tivozanib (Fotivda): RCC
- Vandetanib (Caprelsa): thyroid cancer (MTC)

There are 5 disease states in common among the approved indications of 2 or more oral anti-VEGFs: mCRC, GIST, HCC, RCC, and thyroid cancer (DTC and MTC). Nonetheless, since approved indications are also specific to use as first-line or subsequent therapy, co-treatments, or other clinical characteristics,

the indications may not fully overlap.[*] Several agents have unique approved indications from others: lenvatinib for EC, sunitinib for pNETs, and pazopanib for STS. Only cabozantinib (as Cabometyx) is approved for pediatric patients (to treat thyroid cancer); otherwise, prescribing information (ie, package inserts) for oral anti-VEGFs declare that safety and efficacy have not been established in the pediatric population.

This report is a companion to the previous report completed for intravenous (IV) anti-VEGF therapies (presented in February 2024). Oral anti-VEGFs have several non-overlapping indications with IV anti-VEGFs: EC, GISTs, pNETs, STS, and thyroid cancer. Regarding indicated disease states in common between oral and IV anti-VEGFs (ie, mCRC, HCC, RCC), oral anti-VEGF therapies are guideline preferred over IV anti-VEGF therapy in the setting of RCC[2]; whereas, IV anti-VEGF based therapy, such as with bevacizumab, is guideline preferred over oral anti-VEGF options in the setting of HCC and mCRC.[3,4]

All oral anti-VEGFs are available as a single oral formulation (tablets or capsules), with the exception of cabozantinib. Cabozantinib is available in 2 formulations (tablets and capsules), each approved for a different set of indications. Generics are available for sorafenib, sunitinib, and pazopanib. Oral anti-VEGFs are dosed once daily, except for axitinib and sorafenib with a twice-daily dosing interval.

Guideline Recommendations and Direct Comparative Evidence

Guideline recommendations for the place-in-therapy of oral anti-VEGFs, per the National Comprehensive Cancer Network (NCCN), as well as head-to-head comparative information are summarized below, by disease state. Direct comparative randomized controlled trials (RCTs) of oral anti-VEGFs are available in the setting of advanced HCC and RCC but are lacking for other overlapping approved indications (ie, mCRC, thyroid cancer, and GIST). Head-to-head studies included either sorafenib or sunitinib (older anti-VEGFs) compared to newer agents.

***Advanced HCC*:**

Sorafenib and lenvatinib are NCCN *alternative*[†] first-line options for systemic treatment of advanced HCC. They are recommended secondarily to the combinations of bevacizumab (an IV anti-VEGF) plus atezolizumab or tremelimumab-actl + durvalumab, which are the preferred regimens that have outperformed sorafenib.[4,5] Regorafenib and cabozantinib are recommended only as subsequent-line options (ie, following failure of first-line therapy), consistent with their labeled indications.[4]

---

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

[†] The term "alternative" is used to signify an NCCN recommended option that is secondary in preference to the NCCN designated preferred treatment option(s) for the respective line of therapy. Alternative options are NCCN designated "other recommended regimens" 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 34).[4] The term "first-line" typically means the first systemic therapy to be employed, whereas subsequent therapy (eg, second-line), refers to therapy after a prior (eg, first-line) regimen has failed.

Comparative trials in the setting of HCC have used sorafenib, the former first-line therapy, as the comparator: 2 RCTs compared FDA-approved dosages of lenvatinib to sorafenib, and 1 RCT compared an off-label regimen of cabozantinib (40 mg/day) + atezolizumab to sorafenib**.** Regorafenib has not been compared to other oral anti-VEGFs.

In the REFLECT RCT, lenvatinib demonstrated non-inferiority (but not superiority) to sorafenib for the primary outcome of overall survival (OS).[4] Lenvatinib also outperformed sorafenib for some key secondary outcomes in this study such as for progression-free survival (PFS) and objective response;[6] however, a meta-analysis found a higher risk of grade 3 or higher adverse events with lenvatinib versus sorafenib.[7] In a small RCT among patients with unresectable HCC complicated by portal vein tumor thrombus (PVTT; a complication that occurs in 44%-62% of patients with HCC), lenvatinib demonstrated better outcomes (ie, delayed disease progression and improved objective response rate) compared to sorafenib.[8]

While novel combination regimens are currently being explored for first-line therapy, such as cabozantinib + atezolizumab (currently an off-label combination that outperformed sorafenib for PFS but not for OS[9,10]), the NCCN has yet to include this regimen as a first-line option (as of its 1.2024 guideline).[4]

***Metastatic RCC*:**

For the treatment of metastatic clear cell RCC (ccRCC; comprising about 70% of RCC cases), axitinib, cabozantinib, and lenvatinib are among first-line NCCN preferred drug regimens, as monotherapy and/or in combination regimens, and among subsequent-line treatment regimens for advanced disease.[2] Pazopanib and sunitinib are alternative options for first-line or subsequent-line treatment. Consistent with its approved indication, NCCN recommendations reserve tivozanib for subsequent-line therapy only. For *non-clear cell* RCC (nccRCC), cabozantinib is the only NCCN preferred regimen, while axitinib, lenvatinib (plus everolimus), sunitinib, and pazopanib are options designated as "other recommended" or "useful in certain circumstances".[2]

Apart from tivozanib, newer anti-VEGFs approved for RCC have been compared to the early-approved agents, sorafenib or sunitinib, which were the usual-care therapies in the past. Our literature search located at least 1 comparative RCT for axitinib, pazopanib, sunitinib, or tivozanib *versus sorafenib*; and at least 1 RCT for axitinib (in combination with avelumab or pembrolizumab), cabozantinib (with or without nivolumab), lenvatinib (with pembrolizumab), and pazopanib *versus sunitinib*. Because several newer treatment regimens have demonstrated improved outcomes compared to sunitinib, the NCCN now recommends sunitinib as an "other recommended" first-line option for advanced RCC, rather than a preferred therapy. Despite its approval for RCC, sorafenib is no longer recommended by the NCCN since it has been superseded by other therapies.[2]

Comparisons to Sunitinib Monotherapy: Axitinib + pembrolizumab, cabozantinib + nivolumab, and lenvatinib + pembrolizumab are combinations that are NCCN preferred therapies for first-line treatment of ccRCC.[2] In phase 3 studies for first-line therapy of ccRCC, these combinations outperformed sunitinib with respect to key endpoints of PFS, OS, and objective response.[11-14] Axitinib + avelumab, which is an NCCN "other recommended" regimen for ccRCC first-line therapy[2], outperformed sunitinib with respect

to PFS but did not reduce the overall risk of death.[15] Cabozantinib monotherapy has outperformed sunitinib with respect to PFS and objective response, for first-line therapy for ccRCC and for subsequent treatment of nccRCC;[16,17] thus, it is a preferred option for ccRCC (as first-line) and nccRCC. Pazopanib demonstrated non-inferiority to sunitinib for PFS in ccRCC first-line therapy;[18] it is an NCCN "other recommended regimen," similar to sunitinb.[2]

Comparisons to Sorafenib Monotherapy: With respect to approved indications for first-line therapy of ccRCC, pazopanib outperformed sorafenib with respect to PFS and objective response rate in the SWITCH-2 RCT.[19] Sunitinib appears similar in efficacy (PFS and objective response) to sorafenib, based on independent results from 2 RCTs.[20,21] In the setting of subsequent-line treatment for ccRCC, axitinib (as second-line) and tivozanib (as third- or fourth-line) have outperformed sorafenib with respect to PFS and the percentage of patients achieving an objective response.[22,23]

mCRC:

In the mCRC population, fruquintinib and regorafenib have been exclusively studied in patients who failed first-line systemic therapies. Thus, the NCCN reserves these agents for later-in-line, subsequent therapy after many other options have been tried or are inappropriate. Fruquintinib or regorafenib are recommended for mCRC refractory to oxaliplatin-based and irinotecan-based regimens (some include IV anti-VEGF regimens), as well as biomarker directed therapies, if appropriate.[3]

Thyroid Cancer:

Several oral anti-VEGFs are options for locally recurrent unresectable or metastatic medullary thyroid cancer (MTC) and/or for radioactive iodine (RAI)-refractory differentiated thyroid cancer (DTC). The NCCN guideline prefers lenvatinib for systemic therapy of RAI-refractory DTC; sorafenib is a secondary option, and cabozantinib is a later-in-line option after progressing on lenvatinib and/or sorafenib. The use of other agents *off-label* for RAI-refractory DTC, such as axitinib, pazopanib, sunitinib, and vandetanib, can also be considered if clinical trials and other approved therapies are not available, appropriate, or effective.[24]

For locally recurrent unresectable or metastatic MTC, vandetanib and cabozantinib are among NCCN-preferred systemic therapy options.[24] Off-label use of sorafenib, sunitinib, lenvatinib, or pazopanib can also be considered for symptomatic or progressing MTC if clinical trials and other approved therapies are not available, appropriate, or effective.[24]

GIST:

Sunitinib and regorafenib are NCCN recommended off-label as alternative *first-line* options for unresectable SDH-deficient wild-type GIST (broader than their approved indications for second-line or third-line therapy).[25] For patients with advanced GIST who failed imatinib treatment, sunitinib is a preferred second-line therapy, while regorafenib is a recommended third-line agent after failure of both imatinib and sunitinib. Sunitinib is also recommended in the setting of neoadjuvant treatment. Pazopanib can be used off-label for first-line treatment of SDH-deficient wild-type GIST; and either cabozantinib or pazopanib can be used off-label for later-in-line therapy after FDA-approved therapies have been exhausted for treatment resistant disease.[25]

Other Disease States:

Regarding disease states for which only 1 oral anti-VEGF is FDA approved, sunitinib is among NCCN-preferred options for advanced pNETs, and pazopanib is a preferred option or "other recommended" option for various forms of STS.[26,27] Lenvatinib + pembrolizumab is recommended for recurrent EC (eg, after failing platinum-based therapy).[28] Certain oral anti-VEGFs can be used off-label as second-line or subsequent-line therapy for advanced EC (cabozantinib[28]) or for certain forms of STS (axitinib, sunitinib, sorafenib, and regorafenib).[26,28]

Off-label Uses of Oral Anti-VEGFs

Section 7.0 of this report summarizes recognized off-label uses that are compiled in Micromedex and Lexidrug drug-information compendia, as well as other off-label uses that are not captured in the compendia (eg, additional off-label indications in NCCN guidelines). Off-label uses categorized by Micromedex as "effective" or "evidence favors efficacy" for oral anti-VEGFs are as follows:

- axitinib monotherapy for the treatment of RCC
- lenvatinib with pembrolizumab for the treatment of EC that is deficient mismatch repair (dMMR)
- pazopanib for the treatment of GIST
- regorafenib for the treatment of osteosarcoma
- sorafenib for the treatment of acute myeloid leukemia or GIST
- sunitinib for the treatment of thyroid cancer

Off-label uses that are additionally listed in Lexidrug, but not in Micromedex, include the following:

- axitinib for the treatment of thyroid cancer
- pazopanib for the treatment of desmoid tumors (a type of STS) and thyroid cancer
- sorafenib for the treatment of angiosarcoma (a type of STS)
- sunitinib for the treatment of STS

The off-label uses recognized by Micromedex and Lexidrug are generally congruent with the NCCN guidelines (refer to Table 22), with the exception of lenvatinib for dMMR EC. Refer to the guideline subsections of this report for further details regarding the required clinical criteria for off-label use per the NCCN recommendations for reviewed disease states.

Safety

Oral anti-VEGF therapies have many labeled warnings in common. As a class, they impede wound healing and are associated with a small, elevated risk for hemorrhage, thromboembolic events, and hypertension. Additional warnings for most oral anti-VEGFs are regarding cardiac failure and/or major adverse cardiac events (except cabozantinib); posterior reversable encephalopathy syndrome (except sorafenib); hepatotoxicity (except tivozanib and vandetanib); and thyroid dysfunction or elevation of thyroid stimulating hormone (except regorafenib). More than half[‡] of the oral anti-VEGFs have warnings

[‡] QTc interval prolongation warning for lenvatinib, pazopanib, sorafenib, sunitinib, and vandetanib; gastrointestinal perforation warning for axitinib, cabozantinib, lenvatinib, pazopanib, regorafenib, and sorafenib; renal failure

regarding the potential for QTc prolongation, gastrointestinal perforation, renal failure and/or proteinuria, or dermatologic-related toxicity. There are also many warnings unique to 1 to 3 of the reviewed agents: interstitial lung disease/pneumonitis (for pazopanib and vandetanib), hypocalcemia and/or jaw osteonecrosis (for cabozantinib, lenvatinib, and sunitinib), tumor lysis syndrome (for pazopanib and sunitinib), and adrenal insufficiency (for cabozantinib). Refer to Table 23 and Section 9.1 for more detailed information regarding warnings.

Preferred Drug List Considerations

Anti-VEGF therapies are not yet categorized as preferred or unpreferred on the Utah Medicaid Preferred Drug List (PDL), other than the notation regarding coverage of the brand over generic for sorafenib and sunitinib. A prior authorization is currently in place for anti-VEGF therapies.

NCCN guidelines for cancer therapy are updated frequently; some reviewed for this report have been updated multiple times within the last year. Overall, the NCCN guideline recommendations account for the head-to-head studies that have been completed for on-label uses of oral-anti-VEGFs. In general, agents that are recommended with *top preference by the NCCN* for ***first-line therapy*** and that have the corresponding FDA-indication for the condition could be considered for preference on the Utah Medicaid PDL. NCCN alternative first-line or subsequent-line therapies (or any oral anti-VEGF) may be accessible as a non-preferred product via prior authorization. The following approved agents, for the respective condition, were listed as a ***preferred*** *first-line options* in the NCCN guidelines for reviewed oncologic disorders:

- For *advanced RCC*, axitinib, cabozantinib, and lenvatinib are among first-line NCCN preferred regimens, as monotherapy and/or in combination regimens, and are among subsequent-line regimens for advanced disease.[2]
- For *thyroid cancer*, lenvatinib is a preferred option for systemic therapy of RAI-refractory DTC. Vandetanib or cabozantinib are preferred options for locally recurrent unresectable or metastatic MTC.
    - Some oral anti-VEGFs are recommended off-label as first-line therapy for certain types of thyroid cancer or STS; however, there is also an FDA-approved oral anti-VEGF as an NCCN preferred option in each of these scenarios.
- Regarding disease states for which only 1 oral anti-VEGF is FDA approved, sunitinib is among NCCN preferred options for advanced pNETs, and pazopanib is a preferred option or "other recommended" option for various forms of STS.[26,27]

Of the disease states highlighted in blue, two are among oncologic groups that rank in the top 10 for US cancer-related incidence and/or death rate: kidney cancer and thyroid cancer. While other oral anti-VEGFs may be NCCN alternatives recommended for first-line-therapy of the reviewed disease states, they were listed secondarily in preference compared to the above agents or other agents in different drug classes.

---

and/or proteinuria warning for axitinib, cabozantinib, lenvatinib, pazopanib, sunitinib, tivozanib, and vandetanib; or dermatologic-related toxicity warning for cabozantinib, regorafenib, sorafenib, sunitinib, and vandetanib

1.0 INTRODUCTION

Ten oral vascular endothelial growth factor (VEGF) inhibitors (anti-VEGFs) are approved in the US: axitinib, cabozantinib, fruquintinib, lenvatinib, pazopanib, regorafenib, sorafenib, sunitinib, tivozanib, and vandetanib. Sorafenib, sunitinib, and pazopanib are the oldest of these therapies and are now available as generics. Altogether, approved indications for oral anti-VEGFs encompass many oncologic disorders, including metastatic colorectal cancer (mCRC), endometrial cancer (EC), gastrointestinal stromal tumors (GISTs), hepatocellular carcinoma (HCC), pancreatic neuroendocrine tumors (pNETs), advanced renal cell carcinoma (RCC), advanced soft tissue sarcoma (STS), and thyroid cancer (differentiated [DTC] and medullary [MTC]). While there are 5 indicated disease states in common between 2 or more oral anti-VEGF agents (mCRC, GIST, HCC, RCC, and thyroid cancer), approved indications may not fully overlap due to specificity for use of agents as first-line or subsequent therapy, use with co-treatments,[§] or clinical characteristic requirements (eg, mutational status). Several agents have an approved indicated disease state that is unique from others: lenvatinib for endometrial cancer (EC), sunitinib for pancreatic neuroendocrine tumors (pNETs), and pazopanib for advanced soft tissue sarcoma (STS; **Table 1**). Cabozantinib has 2 formulations, capsules and tablets, each with different strengths and indications; other oral anti-VEGFs are available as a single formulation (**Table 2**).

As a companion to our previously completed Pharmacy and Therapeutics report regarding intravenous (IV) anti-VEGFs (presented in February 2024), this review focuses on oral anti-VEGF approved indications, labeled safety information, and the place-in-therapy according to recent clinical practice guidelines—particularly those by the National Comprehensive Cancer Network (NCCN). A literature search for direct-comparative randomized controlled trial (RCT) evidence was conducted with respect to the US Food and Drug Administration (FDA)-indicated disease states in common between the oral anti-VEGFs, to further inform decision-making regarding the Utah Medicaid Preferred Drug List (PDL). While anti-VEGFs are not on the Utah Medicaid PDL, prior authorization criteria are currently in place for these agents.

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

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

Table 1. Oral Anti-VEGF Products by Indicated Disease State[29-39]

Indication / Agent (Brand)	Colorectal cancer, metastatic (mCRC)	Endometrial cancer (EC)	Gastro-intestinal stromal tumors (GISTs)	Hepatocellular carcinoma (HCC)	Pancreatic neuro-endocrine tumors (pNETs)	Renal cell carcinoma, advanced (RCC)	Soft tissue sarcoma, advanced (STS)	Thyroid cancer (DTC or MTC)
Axitinib (Inlyta)						X (for 1st line and subsequent trt)		
Cabozantinib (Cometriq, Cabometyx)				X (after sorafenib trt)		X		X (advanced or metastatic DTC with progression on anti-VEGF trt, and radioactive iodine-refractory or ineligible; also for progressive, metastatic MTC)[a]
Fruquintinib (Fruzaqla)	X (for later-in-line trt)							
Lenvatinib (Lenvima)		X (advanced disease, pMMR or not MSI-H)		X (for 1st line treatment of unresectable disease)		X (for 1st line and subsequent trt)		X (DTC, locally recurrent or metastatic, progressive, radioactive iodine-refractory)
Pazopanib (Votrient)						X	X	

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

[a] The brand formulation, Cabometyx, is approved for DTC, while the brand, Cometriq, is approved for MTC

Table 1. Oral Anti-VEGF Products by Indicated Disease State[29-39]

Indication / Agent (Brand)	Colorectal cancer, metastatic (mCRC)	Endometrial cancer (EC)	Gastro-intestinal stromal tumors (GISTs)	Hepatocellular carcinoma (HCC)	Pancreatic neuro-endocrine tumors (pNETs)	Renal cell carcinoma, advanced (RCC)	Soft tissue sarcoma, advanced (STS)	Thyroid cancer (DTC or MTC)
Regorafenib (Stivarga)	X (for later-in-line trt)		X (locally advanced, unresectable, or metastatic disease with prior imatinib and sunitinib trt)	X (with prior sorafenib trt)				
Sorafenib (Nexavar)				X (for unresectable disease)		X		X (for locally recurrent or metastatic, progressive, DTC refractory to radioactive iodine)
Sunitinib (Sutent)			X (with progression or intolerance to imatinib)		X (for progressive, well-differentiated pNETs in adults with unresectable locally advanced or metastatic disease)	X		
Tivozanib (Fotivda)						X (advanced, relapsed or refractory disease following 2 or more systemic therapies)		

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

[a] The brand formulation, Cabometyx, is approved for DTC, while the brand, Cometriq, is approved for MTC

Table 1. Oral Anti-VEGF Products by Indicated Disease State[29-39]

Indication / Agent (Brand)	Colorectal cancer, metastatic (mCRC)	Endometrial cancer (EC)	Gastro-intestinal stromal tumors (GISTs)	Hepatocellular carcinoma (HCC)	Pancreatic neuro-endocrine tumors (pNETs)	Renal cell carcinoma, advanced (RCC)	Soft tissue sarcoma, advanced (STS)	Thyroid cancer (DTC or MTC)
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; trt, treatment; VEGF, vascular endothelial growth factor

[a] The brand formulation, Cabometyx, is approved for DTC, while the brand, Cometriq, is approved for MTC

Table 2. Oral Anti-VEGF Formulations[29-39]

Active Ingredient (Initial approval year)	**Brand Name/Strength**
Axitinib (2012)	Inlyta 1 mg, 5 mg tablets
Cabozantinib (2012)	Cometriq 60 mg, 100 mg, 140 mg daily dose capsule pack Cabometyx 20 mg, 40 mg, 60 mg tablets
Fruquintinib (2023)	Fruzaqla 1 mg and 5 mg capsules
Lenvatinib (2015)	Lenvima 4 mg, 8 mg, 10 mg, 12 mg, 14 mg, 18 mg, 20 mg, and 24 mg daily-dose capsule pack (comprised of 4 mg and/or 10 mg capsules)
Pazopanib (2009)	Votrient (*generic available*) 200 mg tablets
Regorafenib (2012)	Stivarga 40 mg tablets
Sorafenib (2005)	Nexavar (*generic available*) 200 mg tablets
Sunitinib (2006)	Sutent (*generic available*) 12.5 mg, 25 mg, 37.5 mg, 50 mg capsules
Tivozanib (2021)	Fotivda 0.89 mg, 1.34 mg capsules
Vandetanib (2011)	Caprelsa 100 mg, 300 mg tablets

2.0 METHODS

The following websites were screened for treatment guidelines regarding cancers applicable to the FDA-approved uses of oral 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 Urological Association (AUA): https://www.auanet.org/guidelines-and-quality/guidelines

V. American Thyroid Association: https://www.thyroid.org/professionals/ata-professional-guidelines/
VI. American Association of Clinical Endocrinology: https://pro.aace.com/clinical-guidance
VII. Lexidrug *Clinical Practice Guidelines* link among drug monographs

The NCCN guidelines were the focus of the review for the guideline information sections of this report because these were the most updated US guidelines for the reviewed indications. Nonetheless, information from ASCO and/or other relatively recent guidelines were also incorporated, as available, particularly for indications where more than 1 oral anti-VEGF therapy is approved.

For product prescribing information (ie, 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 FDA-approved indications in common. The phased approach incorporated searching for and screening of most recently published SRs first, from Ovid-Medline and Epistemonikos[**], then refining the search to later publication years tailored to certain drugs/indications as needed (per the rationale described in Box 1 of Appendix B). 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[40] and Embase[41]). 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 parallel study arms, or individual primary RCTs, directly comparing 2 different oral anti-VEGF products in the setting of approved disease/indications. Direct pair-wise meta-analysis statistical data were eligible for inclusion, or result data from individual RCTs with direct comparisons. Post-hoc exploratory analyses were excluded, along with conference abstracts (ie, only peer-reviewed publications for individual RCTs and prespecified key outcomes were included). Moreover, RCTs comparing an oral-anti-VEGF in an off-

[**] Epistemonikos is a medical literature database consolidating SRs from Cochrane, PubMed, Embase, CINAHL, and other literature database sources.

label regimen were not exhaustively included in the head-to-head comparative section of this report (Section 8.0). 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

Oral anti-VEGF agents inhibit extracellular VEGF receptors on endothelial cells (and most also affect other kinases), ultimately reducing the downstream signaling transduction pathway that stimulates angiogenesis (growth of microvasculature). Blockade of VEGF is thought to impact *certain* cancers by impeding nutrient supply to tumor cells; though there may also be other mechanisms by which these agents inhibit tumor growth (eg, direct effects on tumor cells, or normalization of vessels), effects which may also be unique to the type of cancer.[42] The following bullet points summarize the mechanism of action[††] for the reviewed oral anti-VEGF agents:

- **Axitinib** blocks several VEGF receptors (VEGFRs) including VEGFR-1, -2, and-3 which play a role in angiogenesis and the pathological development of tumor expansion and progression.
- **Cabozantinib** affects VEGFRs (VEGFR-1, -2, and -3) in addition to many other proinvasive tyrosine kinases (eg, AXL, FLT-3, KIT, MER, MET, RET, ROS1, TIE-2, TRKB, TYRO3), thereby inducing cancer cell apoptosis, and suppression of angiogenesis and tumor growth progression.
- **Fruquintinib** inhibits VEGFRs (VEGFR-1, -2, and -3); in vitro studies showed reduced VEGF-mediated endothelial cell proliferation and tubular formation with fruquintinib treatment, and in vivo studies showed inhibited colon tumor growth within a mouse model.
- **Lenvatinib** inhibits VEGFRs (VEGFR-1, -2, and -3) and other tyrosine kinases (fibroblast growth factor (FGF) receptors FGFR-1, -2, -3, and -4, platelet derived growth factor receptor alpha (PDGFRα), KIT, and RET) to suppress tumor growth/progression. Mechanism studies observed lenvatinib inhibited the growth of hepatocellular carcinoma cell lines reliant on FGFR signaling.
- **Pazopanib** blocks VEGFR-1, -2, and -3, along with other tyrosine kinases (FGFR-1 and -3, cKIT, lymphocyte-specific protein tyrosine kinase, PDGFR-α and -β, interleukin-2 receptor-inducible T-cell kinase, and transmembrane glycoprotein receptor tyrosine kinase) to hinder tumor growth by impeding angiogenesis. In vivo mouse models showed pazopanib inhibited angiogenesis and growth of some human tumor xenografts.
- **Regorafenib** inhibits a variety of kinases crucial for oncogenesis and tumor angiogenesis, such as VEFR-1, -2, and -3, RET, KIT, PDGFR- α and β,BRAF, FGFR-1 and -2, DDR2, and TIE2, among others.
- **Sorafenib** targets various cell surface kinases including VEGFR-1, -2, and -3, PDGFR-β, cKIT, RET, and others, in addition to intracellular kinases (BRAF, including mutant BRAF, and c-CRAF), thereby reducing tumor cell proliferation; most of these kinases are implicated in angiogenesis, tumor cell

[††] Cellular/kinase-level effects were demonstrated by biochemical or cellular assays, or animal models with tumor xenografts.

signaling, and apoptosis. Sorafenib inhibited human tumor xenografts of HCC, RCC, and DTC in immunocompromised mice.

- **Sunitinib** inhibits several kinases, including VEGFR-1, -2, and -3, PDGFR-α and -β, KIT, RET, FLT3, and CSF-1R, exhibiting both anti-tumor and anti-angiogenic effects.
- **Tivozanib** blocks the phosphorylation of VEGFR-1, -2, and -3, and has inhibitory effects on PDGFR-β and c-KIT, consequently affecting vascular permeability, angiogenesis, and tumor proliferation. In animal models (mice/rats), treatment with tivozanib inhibited angiogenesis, vascular permeability, and growth in tumor xenograft renal cell carcinoma.
- **Vandetanib** targets various kinase families including VEGFR, epidermal growth factor receptor (EGFR), Src, and EPH, as well as individual RET, TIE2, and BRK kinases. Therefore, this agent blocks tumor angiogenesis, maintenance of the tumor microenvironment, and proliferation. In vivo studies in mouse models showed that vandetanib inhibited tumor mediated angiogenesis, vessel permeability, tumor growth, and metastasis.

4.0 APPROVED INDICATIONS OF ORAL ANTI-VEGF AGENTS

Table 3 shows the clinical scenarios for which oral anti-VEGF agents are indicated, including indication specifications regarding prior treatment, other clinical characteristics, and co-treatments, as applicable. Apart from Cabometyx (cabozantinib), the safety and efficacy of oral anti-VEGF agents have not been established in the pediatric population according to labeled prescribing information (ie, package inserts). Cabometyx (cabozantinib) is approved for 12 years of age and older, for subsequent therapy of advanced differentiated thyroid cancer (DTC).

Of the reviewed oral anti-VEGF agents, lenvatinib has the most approved indications (approved for 4 oncologic disorders). Agents approved for 3 oncologic disorders include cabozantinib, regorafenib, sorafenib, and sunitinib. The remaining agents are approved for 1 or 2 oncologic disorders (1: axitinib, fruquintinib, tivozanib, vandetanib; 2: pazopanib). Of the agents approved for 1 oncologic disorder, fruquintinib and tivozanib are not indicated for first-line systemic therapy (indicated as subsequent therapy only, after failure of several systemic therapies). Oncologic disorders with more than 1 oral anti-VEGF therapy approved for use include thyroid cancer, mCRC, GIST, HCC, and RCC. In general, indications for anti-VEGF products may be specific to clinical characteristics of the cancer, pre-treatment status, and may specify treatment regimen co-treatments; thus, indications for in-common disease states, may not fully overlap[29-39]:

- For thyroid cancer, agents are approved for either medullary thyroid cancer (MTC) or differentiated thyroid cancer (DTC). Two agents are approved for MTC (cabozantinib [as Cometriq formulation] and vandetanib). Three agents are approved for DTC (cabozantinib [as Cabometyx formulation], lenvatinib, and sorafenib). Of these, Cabometyx (cabozantinib) is specified for DTC *subsequent* treatment only after patients have failed a prior anti-VEGF treatment, whereas the agents can be used as first-line systemic therapy for their respective indications.

- For GIST, 2 anti-VEGF therapies are approved for *subsequent* therapy: sunitinib is approved after failure or intolerance to imatinib, while regorafenib is indicated after failing both *sunitinib* and imatinib.
- For advanced HCC, 2 oral anti-VEGFs are approved as *first-line* systemic therapy (sorafenib and lenvatinib), while the others (cabozantinib and regorafenib) are approved for use after *sorafenib* treatment.
- Most oral anti-VEGFs approved for advanced RRC have an indication for first-line systemic therapy (axitinib, cabozantinib, lenvatinib, pazopanib, sorafenib, sunitinib); whereas tivozanib is only approved for subsequent therapy, following prior treatment with 2 or more systemic therapies.
- The 2 agents approved for mCRC, fruquintinib and regorafenib, are both for subsequent-line therapy only, after failing several chemotherapy-based regimens and several other first-line systemic options, including an anti-VEGF-based therapy (ie, with an intravenous anti-VEGF), and an anti-EGFR (for RAS wild-type disease only).

Several disorders have only one oral anti-VEGF agent approved for use: endometrial cancer (EC; lenvatinib), pancreatic neuroendocrine tumors (pNETs; sunitinib), and advanced soft tissue sarcoma (STS; pazopanib). Of these, lenvatinib is for subsequent therapy only, for advanced EC, after a prior systemic therapy has been tried; and pazopanib can be used for STS after failing chemotherapy.

Oral anti-VEGFs are dosed once daily with the exception of axitinib and sorafenib that require a twice daily dosing interval.[29-39] Refer to Table A1 of Appendix A to view the recommended dosing per approved indication.

Table 3. Oral Anti-VEGF Indications [a,29-39]

Agent	Indicated Clinical Scenario
Thyroid cancer (DTC or MTC)	
Cabozantinib	*Cometriq brand*: for progressive, metastatic medullary thyroid cancer (**MTC**) *Cabometyx brand*: for patients 12 years of age and older with locally advanced or metastatic differentiated thyroid cancer (**DTC**) that has progressed following prior VEGFR-targeted therapy and who are radioactive iodine-refractory or ineligible
Lenvatinib	For locally recurrent or metastatic, progressive, radioactive iodine-refractory **DTC**
Sorafenib	For locally recurrent or metastatic, progressive, **DTC** refractory to radioactive iodine treatment
Vandetanib	For symptomatic or progressive **MTC** with unresectable locally advanced or metastatic disease. May use for indolent, asymptomatic or slowly progressing disease after weighing treatment related risks
Colorectal cancer, metastatic (mCRC)	
Fruquintinib Regorafenib	For mCRC in patients (adults specified for fruquintinib) previously treated with oxaliplatin-irinotecan-, and fluoropyrimidine-based chemotherapy, an anti-VEGF therapy (eg, intravenous anti-VEGF), and, if RAS wild-type disease, an anti-EGFR therapy
Endometrial carcinoma (EC)	
Lenvatinib	For advanced endometrial carcinoma that is mismatch repair proficient (pMMR) or not microsatellite instability-high (MSI-H), with disease progression following prior systemic therapy and not a candidate for curative surgery or radiation; used in combination with pembrolizumab
Gastrointestinal stromal tumors (GISTs)	
Regorafenib	For locally advanced, unresectable or metastatic GIST previously treated with imatinib and sunitinib
Sunitinib	For GIST disease progression, in adults, on or after intolerance to imatinib mesylate
Pancreatic neuroendocrine tumors (pNETs)	
Sunitinib	For progressive, well-differentiated pNETs in adults with unresectable locally advanced or metastatic disease
Soft tissue sarcoma (STS)	
Pazopanib	For advanced soft tissue sarcoma already treated with chemotherapy
Hepatocellular carcinoma (HCC)	
Cabozantinib	For HCC in patients previously treated with sorafenib
Lenvatinib	For first-line treatment of unresectable HCC
Regorafenib	For HCC in patients previously treated with sorafenib
Sorafenib	For unresectable HCC

Abbreviations: DTC, differentiated thyroid cancer; GIST, gastrointestinal stromal tumor; HCC, hepatocellular carcinoma; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability-high; MTC, medullary thyroid cancer; pMMR, mismatch repair proficient; pNET, pancreatic neuroendocrine tumors; RCC, renal cell carcinoma; VEGF, vascular endothelial growth factor

Table 3. Oral Anti-VEGF Indications [a,29-39]

Agent	Indicated Clinical Scenario
Renal cell carcinoma (RCC)	
Axitinib	• For first-line treatment of advanced RCC; used in combination with avelumab or pembrolizumab • For use as RCC monotherapy *after failure* of 1 prior systemic therapy
Cabozantinib	• For first-line treatment of advanced RCC; used in combination with nivolumab • For treatment of advanced RCC as monotherapy
Lenvatinib	• For first-line treatment of adults with advanced RCC; used in combination with pembrolizumab • For adults with advanced RCC following 1 prior anti-angiogenic therapy; used in combination with everolimus
Pazopanib	For adults with advanced RCC
Sorafenib	For advanced RCC
Sunitinib	• For adults with advanced RCC, as monotherapy • For adjuvant therapy in adults with high risk of recurrent RCC following nephrectomy
Tivozanib	For relapsed or refractory advanced RCC following 2 or more prior systemic therapies

Abbreviations: DTC, differentiated thyroid cancer; GIST, gastrointestinal stromal tumor; HCC, hepatocellular carcinoma; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability-high; MTC, medullary thyroid cancer; pMMR, mismatch repair proficient; pNET, pancreatic neuroendocrine tumors; RCC, renal cell carcinoma; VEGF, vascular endothelial growth factor

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 with each oral anti-VEGF agent at exposures below the expected human therapeutic exposure[29-39]; refer to **Table 4**. Pregnant women should be advised of the potential risk to a fetus before using any of the oral anti-VEGF agents.

Table 4. Pregnancy Information[29-39]

All Agents	With all agents, animal models demonstrated fetal harm at exposure levels below the expected therapeutic human exposure
Axitinib	in mice: teratogenic, embryo and fetotoxic, skeletal abnormalities observed
Cabozantinib	in rabbits/rats: embryofetal death and structural anomalies observed
Fruquintinib	in rats: embryotoxic and teratogenic effects observed
Lenvatinib	in rabbits/rats: teratogenic, abortifacient, embryo and fetotoxic, structural abnormalities observed
Pazopanib	in rabbits/rats: teratogenic, abortifacient, embryofetal death and structural anomalies
Regorafenib	in rabbits/rats: embryolethal and teratogenic, structural abnormalities observed
Sorafenib	in rabbits/rats: embryotoxicity, structural abnormalities observed
Sunitinib	in rabbits: craniofacial malformations observed • embryolethality and skeletal malformations also observed in rabbits/rats at doses higher than the human exposure (eg, 3-6 times higher)
Tivozanib	in rats: maternal toxicity, embryofetal death, structural and developmental abnormalities observed
Vandetanib	in rats: embryofetal death, fetal malformations observed

With the exception of Cabometyx (cabozantinib), labeled prescribing information (ie, package inserts) for oral anti-VEGFs describe that safety and effectiveness have not been established in the **pediatric population**. Refer to **Table 5** for **renal and hepatic impairment** information for the reviewed agents.

Table 5. Renal and Hepatic Impairment Information[29-39]

Renal dose adjustments
No renal dose adjustment is labeled for axitinib, cabozantinib, fruquintinib, pazopanib, sorafenib, sunitinib, regorafenib, or tivozanib.
For moderate renal impairment:
Vandetanib: decrease the starting dose to 200 mg daily
For severe renal impairment:
Lenvatinib: dose reduce to 10 mg to 14 mg once daily, depending on indication
Not recommended in severe impairment: vandetanib
The following agents have not been studied in severe renal impairment and/or in renal dialysis: cabozantinib, fruquintinib, pazopanib, sorafenib, or regorafenib.
Hepatic dose adjustments
No adjustments specified in labeling: fruquintinib, sorafenib, sunitinib, regorafenib
For mild impairment:
Cabozantinib: reduce the starting dose of Cometriq to 80 mg
For moderate impairment:
Axitinib: reduce the starting dose by half; after the trial on the lower dose, increase or decrease dose based on individual safety and tolerability
Cabozantinib: reduce the Cabometyx dose to 40 mg or to 20 mg, depending on the indication; reduce the starting dose of Cometriq to 80 mg
Pazopanib: dose reduce to 200 mg once daily for moderate hepatic impairment, if alternatives to pazopanib cannot be used
Tivozanib: dose reduce to 0.89 mg per day
Vandetanib: not recommended in moderate or severe hepatic impairment
For severe impairment:
Lenvatinib: Dose reduce to 10 mg to 14 mg once daily, depending on indication
Not recommended in severe hepatic impairment: cabozantinib (as Cabometyx), fruquintinib, pazopanib, regorafenib, and vandetanib
Has not been studied in severe hepatic impairment: axitinib, sorafenib, sunitinib, and tivozanib

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

The following subsections are organized according to overlapping indicated disease states among oral anti-VEGF agents: advanced hepatocellular carcinoma (Section 6.1), advanced renal cell carcinoma (Section 6.2), thyroid cancer (Section 6.3), gastrointestinal stromal tumors (Section 6.4), and metastatic colorectal cancer (Section 6.5). Thereafter, subsections address the remaining FDA-approved indications that are unique to a single oral anti-VEGF (applicable to lenvatinib for endometrial cancer [Section 6.6], sunitinib for pancreatic neuroendocrine tumors [Section 6.7], and pazopanib for soft tissue sarcoma [Section 6.8]).

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

- Hepatocellular Carcinoma guideline (*Version 1.2024— April 2024*)[4]
- Kidney Cancer guideline (*Version 3.2024—March 2024*)[2]
- Thyroid Cancer guideline (*Version 2.2024— March 2024*)[24]
- Gastrointestinal Stromal Tumors guideline (*Version 1.2024—March 2024)*[25]
- Colon Cancer guideline (*Version 1.2024— January 2024*)[43]
- Uterine Neoplasms guideline (*Version 2.2024—March 2024*)[28]
- Neuroendocrine and Adrenal Tumors guideline *(Version 1.2023—August 2023)*[44]
- Soft Tissue Sarcoma guideline *(Version 3.2023—December 2023)*[26]

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 61).[43]
- *Other recommended (ie, alternative)*: (NCCN, page 61).[43]
- *Useful in certain circumstances*: “may be used for selected patient populations” (NCCN, page 61).[43]

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.[45]
- **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).[45] Generally, ICIs “…alter the interaction between immune cells and antigen presenting cells, including tumor cells,…[to]…augment an antitumor immune response” (page 41, NCCN).[2]

6.1 Hepatocellular Carcinoma (HCC)

In 2020, liver cancer was attributed to the sixth highest cancer-related death rate in the US (age-adjusted rate: 6.5 per 100,000 people).[1] This includes hepatocellular cancer (72% of cases) and intrahepatic bile duct cancer (19% of cases). About 41,200 new liver cancer cases are diagnosed each year in the US, and the incidence is about 3 times higher in men than in women.[1,46] The 5-year relative survival rate for liver cancer is 21%.[46] Common sites of metastasis include the lungs, adrenal glands, peritoneum, and bone.[47]

Hepatocellular carcinoma (HCC) 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.[47,48] Thus, HCC is often complicated by related co-morbidities.[47] Approximately two-thirds of cases are diagnosed at 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.[49-51] 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.[51]

Four oral anti-VEGF agents are approved for the treatment of advanced HCC: cabozantinib (as Cabometyx), lenvatinib, regorafenib, and sorafenib. Their indications, however, differ regarding prior treatment failure: lenvatinib and sorafenib can be used for first-line systemic therapy, whereas cabozantinib and regorafenib are specifically indicated following failure on sorafenib treatment. **Table 6** summarizes indications and recommended dosing for these therapies.

Table 6. Oral Anti-VEGF Indications and Dosing for Hepatocellular Carcinoma (HCC)[29,32,33,38]

Cabozantinib (Cabometyx formulation only)	For hepatocellular carcinoma previously treated with sorafenib: • 60 mg once daily
Lenvatinib	For first-line treatment of unresectable hepatocellular carcinoma: • 12 mg once daily for patients ≥60 kg, or 8 mg once daily for patients below 60 kg
Regorafenib	For hepatocellular carcinoma in patients previously treated with sorafenib • 160 mg once daily for the first 21 days of each 28-day cycle
Sorafenib	For unresectable hepatocellular carcinoma • 400 mg twice daily

6.1.1 Key Recommendations for Oral Anti-VEGF Therapy

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[‡‡]).[47] The intravenous anti-VEGF therapy, bevacizumab, is a preferred first-line treatment (in combination with atezolizumab), as this regimen has outperformed the previous long-

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

standing first-line oral agent, sorafenib.[5,47] Tremelimumab-actl with durvalumab is also a preferred option. The 2 oral anti-VEGFs, sorafenib and lenvatinib, are among 'other recommended' first-line options, as monotherapy, and can be used as subsequent therapy; whereas, regorafenib and cabozantinib are only recommended as subsequent-line options, consistent with their labeled indications.[47] **Table 7** summarizes the NCCN guideline recommendations regarding oral anti-VEGF agents for the treatment of HCC.

Table 7. NCCN Liver Cancer Guideline, Oral Anti-VEGF Treatment Recommendations, 2024[a,47]

First-line Systemic Therapy	Subsequent-line Therapy for Disease Progression
Preferred • atezolizumab + bevacizumab (category 1) • tremelimumab-actl + durvalumab (category 1) *Other recommended alternative regimens* • **sorafenib** (category 1) • **lenvatinib** (category 1) • durvalumab (category 1) • pembrolizumab (category 2B)	*Preferred for Child-Pugh Class A* • **regorafenib** (category 1) • **cabozantinib** (category 1) • **lenvatinib** (category 2A) • **sorafenib** (category 2A) *Other recommended for Child-Pugh Class A*: nivolumab + ipilimumab, pembrolizumab *Useful in certain circumstances*: ramucirumab (if AFP ≥400 ng/mL, category 1); nivolumab; dostarlimab for MSI-H/dMMR tumors; selpercatinib for RET gene fusion-positive 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 oral anti-VEGF therapies, several intravenous anti-VEGF therapies are also options, either for (a) first-line systemic therapy (bevacizumab + atezolizumab, a preferred regimen), or for (b) subsequent-line therapy (ramucirumab, as 'useful in certain circumstances' [eg, AFP>400])

Of US treatment guidelines, the NCCN guideline for systemic treatment of HCC was most recently published in 2023, followed by the American Gastroenterological Association (AGA) 2022 guideline and then the 2020 American Society of Clinical Oncology (ASCO) guideline. Similar to the NCCN guideline, the AGA guideline recommends sorafenib and lenvatinib among first-line therapy options, and reserves cabozantinib and regorafenib to second-line therapy after progression of disease on sorafenib, in patients with metastatic HCC with preserved liver function not eligible for locoregional therapies or resection.[52] ASCO recommendations are also similar to the NCCN guideline regarding oral anti-VEGF therapy for first- or second-line systemic treatment.[53]

6.2 Renal Cell Carcinoma (RCC)

Kidney/renal pelvis cancer is attributed to the 9th highest cancer-diagnosis incidence rate in the US (age-adjusted rate: 15.8 per 100,000 people).[1] The majority (85%) of kidney tumors are renal cell carcinomas (RCC) and the majority of RCC cases (70%) are of clear cell histology (ccRCC; affecting renal stem cells and typically the most aggressive form of RCC).[2,54] The remaining RCC cases are grouped into the classification of non-clear cell RCC (nccRCC), a heterogenous histologic group including papillary (10% of all RCC cases) and chromophobic RCC (5% of RCC cases), among others.[2,54] RCC risk factors include smoking, obesity, and hypertension. The disease can also be hereditarily caused by mutations in the von Hippel-Lindau (VHL) gene. Genetic evaluation for RCC is recommended for patients who present with multiple renal masses, who are 46 years old or younger at diagnosis, or who have a family history of RCC.[2]

About 25% of patients with RCC initially present with locally advanced or metastatic disease, and for those with initially localized tumors, 20%–40% eventually metastasize.[54] The most common locations of RCC metastasis are the lungs, bone, liver, lymph nodes, adrenal glands, and the brain.[2] Once advanced, therapies such as surgical tumor excision or nephrectomy are no longer an option as they are for early-stage RCC. Systemic therapy for relapsed or metastatic RCC entails targeted therapies: anti-VEGFs, TKIs, mTOR serine-threonine kinase inhibitors, and immune checkpoint inhibitor monoclonal antibodies (ICI-mAb).[2] Advancements in these therapy options over the years have increased the 5-year survival of advanced RRC from 7.3% (1992–1995) to 15% (2012–2018).[54]

Seven oral anti-VEGF agents are approved for the treatment of advanced RCC: axitinib, cabozantinib, lenvatinib, pazopanib, sorafenib, sunitinib, and tivozanib. Of these, tivozanib is the only agent restricted, per labeled indication, to subsequent-line therapy (ie, not for first-line treatment). **Table 8** summarizes indications and recommended dosing for these therapies.

Table 8. Oral Anti-VEGF Indications and Dosing for Advanced Renal Cell Carcinoma (RCC)[29-35]

Axitinib	For first-line treatment of advanced renal cell carcinoma • 5 mg twice daily, combined with avelumab; may increase axitinib dose after 2 weeks, up to 10 mg twice daily at intervals of 2 weeks or longer • 5 mg twice daily, combined with pembrolizumab; may increase axitinib dose after 6 weeks, up to 10 mg twice daily at intervals of 6 weeks or longer For second-line therapy of advanced renal cell carcinoma after failure of a prior systemic therapy • 5 mg twice daily
Cabozantinib	For first-line treatment of advanced renal cell carcinoma • 40 mg once daily used in combination with nivolumab For treatment of advanced renal cell carcinoma, as monotherapy • 60 mg once daily
Lenvatinib	For first-line treatment of adults with advanced renal cell carcinoma • 20 mg once daily, in combination pembrolizumab For adults with advanced renal cell carcinoma following 1 prior anti-angiogenic therapy • 18 mg once daily, used with everolimus
Pazopanib	For adults with advanced renal cell carcinoma • 800 mg once daily

Table 8. Oral Anti-VEGF Indications and Dosing for Advanced Renal Cell Carcinoma (RCC)[29-35]

Sorafenib	For advanced renal cell carcinoma • 400 mg twice daily
Sunitinib	For adults with advanced renal cell carcinoma, as monotherapy • 50 mg once daily, in a cycle of 4 weeks on treatment followed by 2 weeks off For adjuvant therapy in adults with high risk of recurrent renal cell carcinoma following nephrectomy • 50 mg once daily, in a cycle of 4 weeks on treatment followed by two weeks off, for a total of nine 6-week cycles
Tivozanib	For relapsed or refractory advanced renal cell carcinoma following 2 or more prior systemic therapies • 1.34 mg once daily for the first 21 days of each 28-day cycle

6.2.1 Key Recommendations for Oral Anti-VEGF Therapy

The NCCN guideline specifies treatment regimens for RCC according to tumor histology and prognostic risk stratification.[2] With respect to relapsed or metastatic ccRCC, axitinib, cabozantinib, and lenvatinib are among first-line *preferred* drug regimens: axitinib + pembrolizumab, cabozantinib +/- nivolumab, and lenvatinib + pembrolizumab. These agents are also among recommended subsequent-line options (ie, after failing a first-line regimen), regardless of the prior treatment. Pazopanib and sunitinib are "other recommended" options for first-line treatment of ccRCC and are also alternative options for subsequent treatment. Similar to the approved indication, the NCCN reserves tivozanib to subsequent-line therapy only.[2]

For *non-clear cell* histology metastatic RCC, cabozantinib monotherapy is the only NCCN preferred regimen, while axitinib, lenvatinib, sunitinib, pazopanib are among regimens designated as "other recommended" or "useful in certain circumstances". Although approved for RCC, sorafenib is no longer NCCN recommended for RCC.[2] **Table 9** summarizes the NCCN guideline recommendations regarding oral anti-VEGF agents for systemic treatment of advanced RCC.

Of the US treatment guidelines, the NCCN guideline for the treatment of RCC was most recently published in 2024, followed by the 2022 American Society of Clinical Oncology (ASCO) guideline. Rather than specific recommendations that differentiate preferences between individual anti-VEGFs, the 2022 ASCO guideline for metastatic ccRCC makes generalized recommendations with respect to the anti-VEGF drug class; overall, these recommendations are largely in line with the NCCN guideline. For example, combination therapy with an ICI-mAb is ASCO preferred first-line therapy (ie, ICI plus an anti-VEGF for any risk group or 2 ICI-mAb agents for intermediate- or poor-risk disease); otherwise, monotherapy with an ICI-mAb or anti-VEGF can be considered secondarily to ICI-combination therapy.[55] The difference is that the NCCN guideline also places cabozantinib *monotherapy* as a preferred option for poor- or intermediate-risk ccRCC.

Table 9. NCCN Kidney Cancer Guideline, Oral Anti-VEGF Treatment Recommendations, 2024[2]

<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 alone, 2A):
• Axitinib + pembrolizumab
• Cabozantinib + nivolumab
• Lenvatinib + pembrolizumab
• Ipilimumab + nivolumab (for P/I risk groups)
• Cabozantinib (for P/I risk groups)</td>
<td>Other recommended, category 2A (except cabozantinib, 2B):
• Axitinib + avelumab
• Cabozantinib (for favorable risk group)
• Ipilimumab + nivolumab (for favorable risk group)
• Pazopanib
• Sunitinib
Useful in Certain Circumstances:
• Axitinib (category 2B)
• High-dose IL-2
• Temsiroliums (for P/I risk groups)</td>
<td>Immuno-oncology Naïve, category 2A:
• Axitinib + pembrolizumab
• Cabozantinib
• Cabozantinib + nivolumab
• Lenvatinib + everolimus or pembrolizumab
• Ipilimumab + nivolumab
• Nivolumab
Prior Immuno-oncology, category 2A
• Axitinib
• Belzutifan
• Cabozantinib
• Lenvatinib + everolimus
• Tivozanib
Refer to guideline for options designated as useful in certain circumstances, depending on prior therapy (included is axitinib, cabozantinib, lenvatinib, pazopanib, sunitinib, tivozanib, 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:
• Clinical trial enrollment
• Cabozantinib</td>
<td>Other recommended, category 2A:
• Lenvatinib + everolimus
• Nivolumab
• Nivolumab + cabozantinib
• Pembrolizumab
• Sunitinib</td>
<td>Useful in Certain Circumstances, category 2A except where indicated
• Axitinib
• Bevacizumab (eg, for papillary RCC)
• Bevacizumab + erlotinib (for advanced papillary RCC, including HLRCC)
• Bevacizumab + everolimus
• Erlotinib
• Everolimus
• Nivolumab + ipilimumab (category 2B)
• Pazopanib
• Temsirolimus</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: intravenous anti-VEGF options recommended in the guideline include bevacizumab/biosimilars as a subsequent-line option for ccRCC, or for nccRCC, as 'useful in certain circumstances.'

6.3 Thyroid Cancer, Differentiated (DTC) or Medullary (MTC)

Thyroid cancer, or carcinoma, is two to three times more common in people assigned female at birth.[24] Data from 2020 showed thyroid cancer was attributed to the fifth highest cancer-diagnosis rate in US females (age-adjusted rate: 16.5 per 100,000 women).[1] The lifetime risk of having a thyroid carcinoma diagnosis in the US is 1.2%, and about 43,700 new US cases were expected in 2023. Histologic types of thyroid carcinoma include differentiated thyroid carcinoma (**DTC**; eg, papillary, follicular, and oncocytic), medullary thyroid carcinoma (**MTC**), and anaplastic thyroid cancer (**ATC**; an aggressive undifferentiated tumor). DTC makes up the overwhelming majority of thyroid cancer cases in the US. Based on data between 2011 to 2015, papillary carcinoma (differentiated) was the most commonly diagnosed histology (90%), followed by other differentiated types (follicular, 4.5%; oncocytic, 1.8%), along with medullary carcinoma (1.6%), and anaplastic carcinoma (0.8%). DTC tends to have a favorable prognosis with treatment. The 10-year survival rate is between 90% to 95%. MTC has a high survival rate in stages I-III (5-year survival rate of 93%), but a low rate once in stage IV (5-year survival rate of 28%).[24]

Four oral anti-VEGF agents are approved for the treatment of advanced thyroid cancer, either for DTC and/or MTC. Some evidence also supports the off-label use of certain agents for other histologies (eg, lenvatinib for anaplastic thyroid cancer [ATC][56]).

- For the treatment of DTC, 3 products have FDA approval: cabozantinib (as Cabometyx), lenvatinib, and sorafenib
- For the treatment of MTC, 2 products have FDA approval: cabozantinib (as Cometriq) and vandetanib

Table 10 summarizes indications and recommended dosing for these therapies.

Table 10. Oral Anti-VEGF Indications and Dosing for Thyroid Cancer[29,32,33,36,37]

Cabozantinib	Cometriq brand: for progressive, metastatic medullary thyroid cancer (**MTC**) • 140 mg once daily Cabometyx brand: for adult and pediatric patients 12 years of age and older with locally advanced or metastatic differentiated thyroid cancer (**DTC**) that has progressed following prior VEGFR-targeted therapy and who are radioactive iodine-refractory or ineligible • 60 mg once daily; or 40 mg once daily for pediatric patients with body surface area <1.2 m^2
Lenvatinib	For locally recurrent or metastatic, progressive, differentiated thyroid cancer (**DTC**) refractory to radioactive iodine • 24 mg once daily
Sorafenib	For locally recurrent or metastatic, progressive, differentiated thyroid carcinoma (**DTC**) refractory to radioactive iodine treatment • 400 mg twice daily with food

Table 10. Oral Anti-VEGF Indications and Dosing for Thyroid Cancer[29,32,33,36,37]

Vandetanib	For symptomatic or progressive medullary thyroid cancer (**MTC**) with unresectable locally advanced or metastatic disease. May use for indolent, asymptomatic or slowly progressing disease after weighing treatment related risks • 300 mg once daily

Abbreviations: DTC, differentiated thyroid cancer; MTC, medullary thyroid cancer; VEGFR, vascular endothelial growth factor receptor

6.3.1 Key Recommendations for Oral Anti-VEGF Therapy

The treatment of choice for thyroid carcinoma is surgery (for DTC and MTC), followed by radioactive iodine (RAI) therapy (for DTC only) or other ablative procedures (for DTC or MTC).[24] Oral anti-VEGF inhibitors are an option for locally recurrent, unresectable or metastatic MTC and for RAI-refractory DTC. Although these therapies can improve progression-free survival, they are not curative and have considerable side effects. Generally oral kinase inhibitors are reserved for patients with rapidly progressing and/or symptomatic disease rather than with indolent, asymptomatic disease.[24]

The NCCN guideline prefers lenvatinib for systemic therapy of RAI-refractory **DTC**; sorafenib is a secondary option (other recommended).[24] Guideline authors describe that lenvatinib and sorafenib have not been directly compared to each other, but indirectly, lenvatinib appears to induce better response rates and therefore is the preferred option. Cabozantinib is an option after disease progression on lenvatinib and/or sorafenib. The use of other oral anti-VEGFs off-label for RAI-refractory DTC, such as axitinib, pazopanib, sunitinib, and vandetanib, can also be considered if clinical trials and other approved systemic therapies are not available, appropriate, or effective.[24]

For locally recurrent, unresectable or metastatic **MTC**, vandetanib and cabozantinib are among NCCN preferred systemic therapy options; though, if the carcinoma is RET mutation positive, then selpercatinib or pralsetinib are the preferred agents.[24] The use of other agents off-label, such as sorafenib, sunitinib, lenvatinib, or pazopanib, can also be considered for symptomatic or progressing MTC if clinical trials and other approved systemic therapies are not available, appropriate, or effective.[24] **Table 11** summarizes the NCCN guideline treatment recommendations involving oral anti-VEGF agents for the treatment of thyroid cancer.

Table 11. NCCN Thyroid Cancer Guideline, Oral Anti-VEGF Treatment Recommendations, 2024[24,a]

Recommended regimens are rated as category 2A for level of evidence unless otherwise specified
***Systemic Therapy for Progressive and/or Symptomatic DTC (Papillary Carcinoma, Follicular Carcinoma, or Oncocytic Carcinomas):* for unresectable locally recurrent/persistent disease, and/or disease with soft tissue, bone, or CNS metastasis not amenable to radioactive iodine**
Preferred • **Lenvatinib** (category 1) *Other recommended* • **Sorafenib** (category 1)
Useful in Certain Circumstances • **Cabozantinib**, for progression after lenvatinib and/or sorafenib (category 1 for papillary carcinoma, 2A for follicular and oncocytic) • Larotrectinib or entrectinib for NTRK gene fusion-positive advanced solid tumors • Selpercatinib or pralsetinib RET mutation-positive tumors • Pembrolizumab for TMB-H (≥10 mut/Mb) tumors or for MSI-H or dMMR tumors that have progressed and exhausted alternative options • Dabrafenib + trametinib for BRAF V600E mutation and progression, lacking alternative treatment options • Other therapies are available and can be considered for progressive and/or symptomatic disease if clinical trials or other systemic therapies are not available or appropriate: ○ Eg, **axitinib**, everolimus, **pazopanib**, **sunitinib**, **vandetanib**, vemurafenib [BRAF positive, category 2B], or dabrafenib [BRAF positive, category 2B]
***Systemic Therapy for Unresectable Recurrent or Persistent Locoregional MTC:* for symptomatic or progressing disease by RECIST Criteria**
Preferred • **Vandetanib** (category 1) • **Cabozantinib** (category 1) • Selpercatinib for RET mutation-positive tumors (category 1) • Pralsetinib for RET mutation-positive tumors (category 2B) *Useful in Certain Circumstances* • Pembrolizumab for TMB-H (≥10 mut/Mb) tumors or for MSI-H or dMMR tumors that have progressed and exhausted alternative options
Systemic Therapy for Unresectable Recurrent or Persistent MTC with Distant Metastases
Preferred • **Vandetanib** (category 1) • **Cabozantinib** (category 1) • Selpercatinib for RET mutation-positive tumors (category 1) • Pralsetinib for RET mutation-positive tumors (category 2B) *Other Regimens (for symptomatic or progressing disease)* • **Sorafenib, sunitinib, lenvatinib, or pazopanib** if a clinical trial or preferred options are not available or appropriate • Dacarbazine-based chemotherapy
Useful in Certain Circumstances • Pembrolizumab for TMB-H (≥10 mut/Mb) tumors or for MSI-H or dMMR tumors that have progressed and exhausted alternative options

Abbreviations: dMMR, mismatch repair deficient; DTC, differentiated thyroid carcinoma; MSI-H, high microsatellite instability; MTC, medullary thyroid carcinoma; mut/MB, mutations/megabase; RECIST, Response Evaluation Criteria in Solid Tumors; TMB-H, tumor mutational burden-high

[a] 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 still uniform NCCN consensus; Category 2B is based upon lower-level evidence, and majority consensus.

6.4 Gastrointestinal Stromal Tumors (GISTs)

Gastrointestinal stromal tumors (GISTs) are a type of soft tissue sarcoma, with a US incidence rate of 0.68 to 0.78 per 100,000 persons.[25] Most GISTs originate in the stomach (60%) or small intestine (30%) but can occur anywhere within the gastrointestinal tract. The most common sites of metastasis include the liver and/or peritoneal surfaces.[25]

GISTs primarily result from genetic mutations of KIT (80%) or PDGFRA (5-10%) receptor tyrosine kinases.[25] Cases without detectable KIT or PDGFRA mutations (5-10%) are referred to as *wild-type* GISTs. KIT and PDGFRA mutational status is predictive of response to TKIs for the treatment of advanced or metastatic GISTs. Thus, molecular testing for such pathogenic variants are recommended when considering TKI therapy. If KIT and PDGFRA mutations are not identified (as in wild-type GISTs), then screening should be conducted for succinate dehydrogenase (SDH) status. SDH-deficiency corresponds to SDH mutations and resistance to the first-line systemic therapy, imatinib. For wild-type GISTs, screening for other pertinent mutations relevant to targeted therapies may also be considered, including NF1, BRAF, NTRK, and FGFR mutations; these occur in a minority of tumors that lack KIT and PDGFRA mutations.[25]

Two oral anti-VEGF agents are approved for the treatment of GISTs: regorafenib and sunitinib. Both are approved for subsequent-line systemic therapy, after failing imatinib (for both) and sunitinib (for regorafenib). **Table 12** summarizes indications and recommended dosing for these therapies.

Table 12. Oral Anti-VEGF Indications and Dosing for Gastrointestinal Stromal Tumors (GISTs)[34,38]

Regorafenib	For locally advanced, unresectable or metastatic GIST previously treated with imatinib and sunitinib • 160 mg once daily for the first 21 days of each 28-day cycle
Sunitinib	For GIST progression in adults, on or after intolerance to imatinib mesylate • 50 mg once daily for 4 weeks, followed by 2 weeks off treatment, until disease progression or unacceptable toxicity

6.4.1 Key Recommendations for Oral Anti-VEGF Therapy

Broader than their approved indications, sunitinib and regorafenib are NCCN recommended options for *first-line* therapy of SDH-deficient wild-type GIST, in addition to being recommended as subsequent-line therapies for unresectable, recurrent, or metastatic GIST.[25] For patients who failed imatinib (first-line therapy for GIST with most KIT or PDGFRA mutations), sunitinib is the preferred second-line therapy, while regorafenib is a recommended third-line therapy after failure of both imatinib and sunitinib. Sunitinib is also recommended in the setting of neoadjuvant treatment of SDH-deficient GIST (ie, prior to surgical resection to reduce the tumor size/surgical morbidity).[25]

The two oral anti-VEGF agents, pazopanib and cabozantinib—which do not have an FDA-approved indication for GIST—are also included among the NCCN guideline.[25] Like sunitinib and regorafenib, pazopanib, can also be considered for first-line therapy of SDH-deficient wild-type GIST, supported by a

phase II RCT. Regarding imatinib-resistant disease, pazopanib and cabozantinib can be considered for later-in-line therapy after other approved/appropriate therapies have been exhausted (based on phase II RCT supportive evidence).[25] **Table 13** summarizes the NCCN treatment recommendations regarding anti-VEGF therapy for GISTs.

Table 13. NCCN GISTs Guideline, Oral Anti-VEGF Treatment Recommendations, 2024[25]

Neoadjuvant Therapy for Resectable Disease with Significant Morbidity	
Preferred; C2A: • Imatinib (for KIT or PDGFRA mutations) • Avapritinib (for PDGFRA exon 18 mutations insensitive to imatinib)	*Useful in certain circumstances; C2A:* • **Sunitinib** (for SDH-deficient) • Larotrectinib (for NTRK mutation) • Dabrafenib + trametinib (for BRAF mutation)
Systemic Therapy for Unresectable, Progressive, or Metastatic GIST	
First Line	
Preferred: • Imatinib (for sensitive mutations; C1)	• Avapritinib (for PDGFRA exon 18 mutations (eg, D842V) insensitive to imatinib; C2A)
Useful for SDH-deficient GIST: • **Sunitinib** (C2A) • **Regorafenib** (C2A) • **Pazopanib** (C2A) • Imatinib + binimetinib (C2B)	• Imatinib + binimetinib (C2B) • Refer to guideline for other 'useful in certain circumstances regimens
Second Line	
Preferred, following imatinib: • **Sunitinib** (C1) • Ripretinib (if intolerant to sunitinib; C2A)	*Preferred, following avapritnib:* • Dasatinib (C2A)
Third Line & Fourth Line	
Preferred, following imatinib/sunitinb: • **Regorafenib** for third-line therapy (C1) • Ripretinib for fourth-line therapy (if not previously received (C1)	
Additional Options After Progression on Approved Therapies, Based on Mutational Status; all C2A:	
• Avapritnib • **Cabozantinib** • **Sorafenib**	• Nilotinib • **Pazopanib** • Ripertinib • Ponatinib • Everolimus + (imatinib, sunitinib, or regorafenib)

Abbreviations: C1, category 1; C2A, category 2A; C2B, category 2B; GISTs; gastrointestinal stromal tumors; 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 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). Utah rates are generally lower than national rates (age-adjusted incidence rate of CRC is 27).[1] Approximately 50-60% of CRC cases progress to metastatic disease, most often spreading to the liver and sometimes to the lungs.[3] The 5-year survival rate of mCRC is 14%.[46] Risk factors for CRC include having a first-degree relative with CRC; 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.[3]

Biomarkers guide pharmacotherapy 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]).[3] It is recommended for molecular testing to be done via broad molecular profiling with next-generation sequencing (NGS), since this genetic platform allows for identification of other rare actional driver mutations that can influence treatment decisions (eg, POLE/POLD1, RET, and NTRK mutations).[43] The following bullets describe key mutation/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[57]
  - MMR or MSI status testing is recommended to characterize all patients with colon cancer[3]
  - 15% of CRC cases are dMMR/MSI[57]
- 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[3]
  - 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[3]
- BRAF gene mutation: genetic mutation of type V600E
  - Testing for BRAF mutation is recommended in all patients with mCRC[3]
  - 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[3]
- HER2 positive: overexpression of HER2 protein
  - Testing is reserved to cases without RAS or BRAF mutations (ie, *wild-type* BRAF and *wild-type* RAS)[3]
  - Approximately 3% of CRC cases are HER2 positive
  - Anti-HER2 therapy is indicated in HER2-amplified tumors that are RAS/BRAF wild-type (WT; ie, negative for RAS/BRAF CRC-related mutations)[3]
- POLE/POLD1 mutations
  - These refer to polymerase gene mutations that cause loss of function in subunits of the enzyme responsible for DNA proofreading/correction of mispaired bases during DNA replication.[43]
  - POLE mutations occur in about 2%–8% of CRC cases that are predominately MSS/pMMR. POLD1 mutations are extremely rare.[43]

- Generally, patients with these mutations have a favorable prognosis and respond well to ICI therapy.[43]
- Other mutational biomarkers exist but present less frequently, such as NTRK fusions (0.35% of CRC cases; may indicate treatment with entrectinib or larotrectinib), and RET fusions (<1% of cases; may indicate selpercatinib treatment).[3]

Fruquintinib and regorafenib are the oral anti-VEGFs approved for the treatment of mCRC; however, their indication is for treatment-resistant disease (including following failure of an intravenous anti-VEGF agent approved for mCRC; eg, bevacizumab). **Table 14** shows the indication and recommended dosing for fruquintinib and regorafenib.

Table 14. Oral Anti-VEGF Indications and Dosing for Metastatic Colorectal Cancer (mCRC)[38,39]

Fruquintinib	For adults with metastatic colorectal cancer previously treated with oxaliplatin-, irinotecan-, and fluoropyrimidine-based chemotherapy, an anti-VEGF therapy (eg, intravenous anti-VEGF), and, if RAS wild-type disease, an anti-EGFR therapy • 5 mg orally daily for the first 21 days of each 28-day cycle
Regorafenib	For patients with metastatic colorectal cancer previously treated with oxaliplatin-, irinotecan-, and fluoropyrimidine-based chemotherapy, an anti-VEGF therapy (eg, intravenous anti-VEGF), and, if RAS wild-type disease, an anti-EGFR therapy • 160 mg once daily for the first 21 days of each 28-day cycle

6.5.1 Key Recommendations for Oral Anti-VEGF Therapies

Unlike intravenous anti-VEGF therapies that are recommended either first-line (eg, bevacizumab-based regimens) or for early subsequent-line therapy, fruquintinib and regorafenib are reserved for later-in-line subsequent therapy after many other options have been tried (or are inappropriate).[43] This is because fruquintinib and regorafenib have been exclusively studied in patients with disease progression on previous standard systemic therapies. In general, the NCCN recommends fruquintinib or regorafenib as options for mCRC refractory to oxaliplatin-based and irinotecan-based regimens (some include IV anti-VEGF combinations), and biomarker directed therapies, as appropriate (for pMMR/MSS disease) ineligible for checkpoint inhibitor immunotherapy).[43]

The NCCN 2024 guideline (**Table 15**) is the most recently published US guideline for treatment selection for advanced CRC. The 2022 ASCO guideline for the treatment of CRC does not mention regorafenib or fruquintinib.[58]

Table 15. NCCN Colorectal Cancer Guideline, Oral Anti-VEGF Treatment Recommendations, 2024[43,a]

Recommended regimens below are rated as category 2A for level of evidence[b]

- **For pMMR/MSS advanced or metastatic CRC (or dMMR/MSI-H or POLE/POLD1 mutation disease that is ineligible for or with progression on ICIs)**:
  - ***Initial treatment following prior oxaliplatin- and irinotecan-based treatment*:**
    - If KRAS/NRAS/BRAF WT: (cetuximab or panitumumab) with or without irinotecan
    - Or use other biomarker directed therapy if appropriate; refer to guideline for directed therapies for BRAF, HER2, KRAS, NTRK, and RET pathogenic variants
  - ***For disease that has progressed through all available/appropriate regimens***
    - trifluridine + tipiracil with or without bevacizumab
    - **regorafenib**
    - **fruquintinib**

Abbreviations: CAPEOX, oxaliplatin + capecitabine; dMMR, deficient mismatch repair; FOLFIRI, leucovorin + fluorouracil + irinotecan; FOLFOX; leucovorin + fluorouracil + oxaliplatin; FOLFIRINOX, leucovorin + fluorouracil + irinotecan + oxaliplatin; ICIs, immune checkpoint inhibitors; MSI-H, microsatellite instability-high; 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; famtrastuzumab 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] *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 still uniform NCCN consensus*

Note: aside from the oral anti-VEGF therapies, the intravenous anti-VEGF therapies (bevacizumab, ramucirumab, and ziv-aflibercept) also have a place in therapy for colorectal cancer

6.6 Approved Indication Unique to Lenvatinib: Endometrial Cancer (EC)

Endometrial cancer (EC), which originates in the endometrium or inner lining of the uterus, is the most common malignancy affecting the female reproductive tract in the US.[28] Uterine cancer is attributed to the fourth highest cancer-related incidence rate in US females. The incidence rate of new cases and deaths from uterine cancer is 27.6 and 5.1, respectively, per 100,000 women (based on 2016-2020 data).[59] Most cases (67%) present with EC located within the uterus at the time of diagnosis.[28] Patients often seek treatment for early-stage EC due to abnormal vaginal bleeding, with symptoms usually presenting during the postmenopausal period. Typically, the prognosis of EC is favorable with a 5-year survival rate of 81%[59], but there are histologies with a higher risk of mortality (eg, clear cell carcinoma, undifferentiated carcinoma, carcinosarcomas, serous carcinoma). EC risk factors include increased estrogen levels (eg, stemming from factors such as obesity, diabetes, and unopposed estrogen use), nulliparity, tamoxifen use, early onset of menarche, delayed onset of menopause, age 55 years or older, and Lynch syndrome.[28]

Biomarker-directed pharmacotherapy may be used for the treatment of EC disease, if applicable. The NCCN guideline recommends MMR testing (or MSI, if results are equivocal) for all patients with EC.[28] HER2 testing is recommended for serous carcinomas and carcinosarcomas (high-risk neoplasms) and can be considered for p53 abnormal carcinomas. For those with recurrent disease or advanced disease (stage III or IV), estrogen and progesterone receptor testing should also be performed.[28]

Lenvatinib is the only oral anti-VEGF approved for the treatment of EC; it is approved for use in combination with pembrolizumab for cases that have failed other systemic therapies and are ineligible for surgery or radiation. **Table 16** shows the labeled indication and dosing of lenvatinib for EC treatment.

Table 16. Lenvatinib Indication and Dosing for Endometrial Cancer (EC)[32]

For advanced disease that is mismatch repair proficient (pMMR) or not microsatellite instability-high (MSI-H), with disease progression following prior systemic therapy and not a candidate for curative surgery or radiation: • 20 mg once daily in combination with pembrolizumab

6.6.1 Key Recommendations for Oral Anti-VEGF Therapy

Platinum-based regimens (eg, carboplatin + paclitaxel) are the preferred first-line systemic therapy for EC.[28] Lenvatinib, in combination with pembrolizumab, is among recommended options for recurrent disease, specifically for pMMR tumors in patients who have previously taken a platinum-based regimen. Other oral anti-VEGF therapy recommended by the NCCN includes cabozantinib (off-label) for second-line or subsequent treatment of recurrent EC.[28] **Table 17** summarizes NCCN recommendations regarding oral anti-VEGF therapy for the treatment of EC.

Table 17. NCCN Uterine Cancer Guideline, Oral Anti-VEGF Treatment Recommendations, 2024[28,a]

Recommended regimens are rated as category 2A for level of evidence unless otherwise specified

Primary or Adjuvant Systemic Therapy for Endometrial Carcinoma (EC) (for stage I-IV unless otherwise noted)

Preferred:

- Carboplatin + paclitaxel + pembrolizumab (for stages III-IV, except carcinosarcoma; C1)
- Carboplatin + paclitaxel + trastuzumab (stage III or IV HER2+ serous uterine carcinoma or carcinosarcoma)
- Carboplatin + paclitaxel + dostrarlimab-gxly (stages III-IV; C1)
- Carboplatin + paclitaxel

Systemic Therapy for Recurrent Endometrial Carcinoma (EC)

First line (can also be used as second-line or subsequent therapy):

Preferred:

- Carboplatin + paclitaxel (C1 for carcinosarcoma)
- Carboplatin + paclitaxel + pembrolizumab (except for carcinosarcoma; C1)
- Carboplatin + paclitaxel + dostarlimab-gxly (C1)
- Carboplatin + paclitaxel + trastuzumab (for HER2+ uterine serous carcinoma or carcinosarcoma)

Useful in certain circumstances (after platinum-based therapy[b]):

pMMR tumors:

- **Lenvatinib** + pembrolizumab (C1)

TMB-H tumors:

- Pembrolizumab

MSI-H/dMMR tumors:

- Pembrolizumab
- Dostarlimab-gxly

Other recommended:

- Carboplatin + docetaxel
- Carboplatin + paclitaxel + bevacizumab

Additional second-line or subsequent options:

Other recommended[c]*:*

- **Cabozantinib**
- Cisplatin + doxorubicin
- Cisplatin + doxorubicin + paclitaxel
- Carboplatin
- Topotecan
- Bevacizumab
- Docetaxel (C2B)

Useful in certain circumstances:

pMMR tumors

- **Lenvatinib** + pembrolizumab (C1)

MSI-H/dMMR tumors

- Avelumab, nivolumab, dostarlimab, or pembrolizumab

HER2+ tumors (IHC 3+ or 2+)

- Fam-trastuzumab deruxtecan-nxki

NTRK gene fusion+ tumors

- Larotrectinib or entrectinib

Abbreviations: C, category; dMMR, mismatch repair deficient; MSI-H, high microsatellite instability; NCCN, National Comprehensive Cancer Network; pMMR, proficient mismatch repair; TMB-H, high tumor mutational burden

[a] *Evidence/Consensus Category 1 (C1): recommendation is based upon high-level evidence and a uniform NCCN consensus; Category 2A (C2A): based on lower-level evidence, but with still uniform NCCN consensus; Category 2B (C2B): based on lower-level evidence, and majority consensus.*

[b] *Platinum-based regimens in any manner, including as adjuvant or neoadjuvant therapy.*

[c] *See the guideline for a complete list of other recommended regimens for second-line or subsequent therapy.*

6.7 Approved Indication Unique to Sunitinib: Pancreatic Neuroendocrine Tumors (pNETs)

Neuroendocrine tumors (NETs) arise from cells of the endocrine system. Pancreatic neuroendocrine tumors (pNETs) are a subset of the most common neuroendocrine tumors, others being gastrointestinal, bronchopulmonary, or thymus derived.[44] Yet, pNETs "…account for approximately 1% of pancreatic cancers by incidence and 10% of pancreatic cancers by prevalence" (NCCN page 144).[44] Overall, prognosis tends to be favorable (5-year survival rate: approximately 50%), especially for locoregionally confined tumors.[60] Risk factors for pNETs include smoking, alcohol use, family history of cancer (usually first-degree relative), diabetes (predominately type 2), chronic pancreatitis, and certain inherited genetic syndromes (ie, multiple endocrine neoplasia type 1, Von Hippel-Lindau syndrome, and neurofibromatosis type 1).[61,62]

pNETs are classified as either non-functional (40% to 91% of pNET cases) or functional.[44] Functional pNETs are hormone producing and lead to hormonal hypersecretory syndromes (ie, gastrinoma, glucagonoma, insulinoma, VIPoma); whereas, non-functional pNETs are usually associated with non-hormone-related symptoms (eg, nausea, weight loss, jaundice, abdominal pain).[27]

Sunitinib is the only anti-VEGF therapy approved for the treatment of pNETs. It is approved for adults with unresectable locally advanced or metastatic progressive, well-differentiated pNET. **Table 18** shows the label indication and dosing of sunitinib for pNETs.

Table 18. Sunitinib Indication and Dosing for Pancreatic Neuroendocrine Tumors (pNETs)[34]

For adults with unresectable locally advanced or metastatic progressive, well-differentiated pNETs: • 37.5 mg once daily

6.7.1 Key Recommendations for Oral Anti-VEGF Therapy

Sunitinib is the only anti-VEGF therapy recommended for use for pNET among the 2023 NCCN guideline for the treatment of pNETs.[44] It is a preferred option for subsequent treatment of locoregional advanced and/or distant metastasized, well-differentiated grade 1 or 2 pNETs that have progressed on front-line therapy (eg, octreotide or lanreotide). It is also recommended for locally advanced or metastatic, well-differentiated, unresectable grade 3 pNETs with favorable biology (eg, slow growing) and disease progression or significant tumor burden.[44] **Table 19** summarizes NCCN recommendations regarding anti-VEGF therapy for the treatment of pNETs.

Table 19. NCCN NET Guideline, Oral Anti-VEGF Treatment Recommendations, 2023[44,a]

Recommended regimens are rated as category 2A for level of evidence unless otherwise specified	
Systemic Treatment for Well-differentiated (Grade 1 or 2), Locoregional Advanced and/or Distant Metastatic pNETs	
Preferred: • For SSTR+ tumors, octreotide LAR or lanreotide[b] • **Sunitinib** (C1 for progressive disease) • Everolimus (C1 for progressive disease) • Temozolomide and capecitabine (preferred for when a decrease in symptoms or debulking is needed) • Peptide receptor radionuclide therapy with lutetium 177 for SSTR+ tumors, with progression on lanreotide or octreotide LAR	*Useful in Certain Circumstances:* • Above-label dosing of lanreotide (up to 120 mg every 2 weeks) or octreotide LAR (up to 60 mg monthly) for SSTR+ tumors with progression on standard dosing • For *VHL* mutations, belzutifan can be considered for patients with progressive pNETs • Radiation therapy ± fluoropyrimidine-based chemotherapy for locally advanced unresectable disease
Other recommended (for symptomatic, bulky, and/or progressive disease):	
• FOLFOX (leucovorin, fluorouracil, and oxaliplatin)	• CAPEOX (capecitabine and oxaliplatin)
Well-differentiated (Grade 3), Unresectable, Locally Advanced or Metastatic NETs, with Favorable Biology[c] and Disease Progression or Clinically Significant Tumor Burden	
• Clinical trial preferred • **Sunitinib** (***pNETs only***) • Chemotherapy (eg, FOLFOX, cisplatin + etoposide, CAPEOX) • Pembrolizumab for tumors that are dMMR, MSI-H, or TMB-H (≥10 mut/Mb)	• Everolimus • Octreotide LAR or lanreotide for SSTR+ tumors and/or hormonal symptoms; above-label dosing may be used for progression on standard dosing (C2B) • Peptide receptor radionuclide therapy with lutetium Lu 177 for SSTR+ tumors • Radiation therapy ± fluoropyrimidine-based chemotherapy for locally advanced unresectable disease

Abbreviations: C, category; dMMR, mismatch repair deficient; LAR, long-acting release; MSI-H, high microsatellite instability; NCCN, National Comprehensive Cancer Network; NETs, neuroendocrine tumors; pNETs, pancreatic neuroendocrine tumors; PET, positron emission tomography; SSTR, somatostatin receptor; TMB-H, high tumor mutational burden

[a] *Evidence/Consensus Category 1 (C1): recommendation is based upon high-level evidence and a uniform NCCN consensus; Category 2A (C2A): based on lower-level evidence, but with still uniform NCCN consensus; Category 2B (C2B): based on lower-level evidence, and majority consensus.*

[b] *Font-line treatment is typically octreotide LAR or lanreotide; however, the guideline algorithm comments that in some cases other systemic recommended options can be started prior to or concurrently with octreotide or lanreotide. For subsequent therapy for non-functional tumors, octreotide LAR or lanreotide should be discontinued, whereas for functional tumors, these agents should be continued in combination other subsequent treatment options.*

[c] *Favorable biology includes tumors that are slow growing, have a Ki-67 <55%, or have positive SSTR-based PET imaging.*

The 2023 ASCO guideline for the treatment of metastatic gastroenteropancreatic NETs is consistent with the NCCN guideline with respect to inclusion of sunitinib among recommended options for grade 1, 2, or 3 pNETs.[63] However, the ASCO guideline is more specific regarding the order of therapy based on somatostatin receptor (SSTR) status. For SSTR-positive pNETs, a somatostatin analog (ie, octreotide or lanreotide) is the preferred first-line therapy; sunitinib is typically a second-line option. For SSTR-negative pNETs, sunitinib can be used first-line (as well as everolimus or chemotherapy) or as a subsequent-line option.[63]

6.8 Approved Indication Unique to Pazopanib: Advanced Soft Tissue Sarcoma (STS)

Soft tissue sarcomas (STS) are a broad group of cancers encompassing over 50 different histologic types that originate from various mesenchymal tissues including adipose, muscle, neural, vascular, or connective tissues.[26] STS primarily manifests in the extremities (arms and legs, 43%) but can occur in other locations (eg, trunk, 10%; visceral, 19%; retroperitoneum, 15%; head/neck, 9%). STS is rare in adults (<1% of adult cancers; and <15% of childhood cancers). Approximately 13,000 Americans were estimated to have the condition in 2022, resulting in about 5,000 fatalities in 2022. Risk factors for STS include previous radiation therapy to the affected region, genetic syndromes (eg, neurofibromatosis, Carney-Stratakis syndrome, Li-Fraumeni syndrome, hereditary retinoblastoma), and exposure to certain chemicals (eg, herbicides). STS tends to metastasize to the lungs, but depending on the location of origin and histological subtype, can disseminate to other areas of the body.[26]

Pazopanib is the only oral anti-VEGF agent approved for the treatment of advanced STS, specifically for adults who have previously received chemotherapy. A labeled limitation of use, however, is that it is unestablished for treatment of adipocytic STS or GISTs. **Table 20** shows the labeled indication and dosing of pazopanib for the treatment of STS.

Table 20. Pazopanib Indication and Dosing for Advanced Soft Tissue Sarcoma (STS)[35]

For adults with advanced disease previously treated with chemotherapy: • 800 mg once daily without food (at least 1 hour before and 2 hours after eating) until no longer tolerable or disease progression.

6.8.1 Key Recommendations for Oral Anti-VEGF Therapy

Several oral anti-VEGF agents are included in the NCCN guideline for the treatment of STS. Of these, pazopanib is recommended for the treatment of most STS histologies.[26] For non-subtype-specific STS (ie, general STS), pazopanib is recommended as first-line treatment for patients unsuitable for IV or anthracycline-based regimens, and as a preferred second-line option (as monotherapy or in combination with gemcitabine) for advanced or metastatic disease (see **Table 21**). With respect to histologic-specific subtypes, pazopanib is a preferred option for desmoid tumors (ie, aggressive fibromatosis), alveolar soft part sarcoma, and solitary fibrous tumors; and is an "other recommended" option for angiosarcoma and dermatofibrosarcoma protuberans with fibrosarcomatous transformation.[26] Other oral anti-VEGFs are recommended *off-label* for STS, including regorafenib, axitinib, sunitinib, and sorafenib.[26] Regorafenib is considered a subsequent-line option for advanced or metastatic STS (non-subtype-specific) and can be

considered for certain angiosarcoma cases. Sorafenib and sunitinib are also recommended as "useful in certain circumstances" for angiosarcoma and are preferred options for solitary fibrous tumors. Other than pazopanib, sorafenib is the only other oral anti-VEGF recommended as a preferred option (category 1) for advanced or unresectable desmoid tumors. Axitinib (in combination with pembrolizumab) is recommended for alveolar soft part sarcoma, as a preferred regimen (in addition to pazopanib).[26]

Table 21. NCCN Soft Tissue Sarcoma Guideline, Oral Anti-VEGF Treatment Recommendations, 2023[26,a]

Recommended regimens are rated as category 2A for level of evidence unless otherwise specified

Systemic Treatment Regimens for General Soft Tissue Sarcoma, Non-histologic Specific

First-line Treatment for Advanced or Metastatic Disease

Preferred:

- Anthracycline-based regimen (eg, with doxorubicin or epirubicin)
- For *NTRK* gene fusion+ sarcomas: larotrectinib or entrectinib

Other recommended:

- Gemcitabine-based regimens (eg, gemcitabine + vinorelbine, docetaxel, or dacarbazine)

Useful in certain circumstances:

- For patients who are unsuitable for IV treatment or anthracycline-based regimens: **pazopanib**
- MAID (mesna, doxorubicin, ifosfamide, and dacarbazine)
- For LMS: trabectedin and doxorubicin
- For *RET* gene fusion+ sarcomas: selpercatinib

Subsequent-line Treatments for Advanced or Metastatic Disease

Preferred:

- **Pazopanib**
- Eribulin (C1 for liposarcoma)
- Trabectedin (C1 for liposarcoma and LMS)

Useful in certain circumstances:

- For dMMR or MSI-H tumors (irrespective of STS subtype): pembrolizumab
- For myxofibrosarcoma, dedifferentiated liposarcoma, cutaneous angiosarcoma, undifferentiated pleomorphic sarcoma, other undifferentiated sarcomas, or TMB-H tumors (≥10 mut/Mb; irrespective of STS subtype): pembrolizumab or nivolumab ± ipilimumab

Other recommended:

- Gemcitabine and **pazopanib** (C2B)
- Gemcitabine and vinorelbine
- Ifosfamide
- Gemcitabine
- Gemcitabine and dacrbazine
- Temozolomide
- **Regorafenib**
- Gemcitabine and docetaxel
- Dacarbazine
- Vinorelbine

Histologic-specific Regimens for STS

Alveolar Soft Part Sarcoma

Preferred:

- **Sunitinib**
- **Pazopanib**
- Pembrolizumab ± **axitinib**
- Atezolizumab

Angiosarcoma

Preferred:	*Other recommended:*	*Useful in certain circumstances:*

Table 21. NCCN Soft Tissue Sarcoma Guideline, Oral Anti-VEGF Treatment Recommendations, 2023[26,a]

• Paclitaxel • For non histologic-specific STS: gemcitabine- or anthracycline-based regimens	• **Pazopanib** • Vinorelbine • Docetaxel	• **Regorafenib** • **Sunitinib** • For cutaneous angiosarcoma: pembrolizumab	• **Sorafenib** • Bevacizumab • Ipilimumab and nivolumab
Desmoid Tumors (Aggressive Fibromatosis)			
Preferred: • **Pazopanib** • **Sorafenib (C1)** • Nirogacestat (C1) • Methotrexate + vinorelbine or vinblastine	• Imatinib • Liposomal doxorubicin • Doxorubicin ± dacarbazine		*Useful in certain circumstances:* • Sulindac or other NSAIDs for pain
Dermatofibrosarcoma Protuberans with Fibrosarcomatous Transformation			
Preferred: • Imatinib	*Other recommended:* • For patients who are unsuitable for IV treatment or anthracycline-based regimens: **pazopanib** • Anthracycline- or gemcitabine-based regimens (eg, doxorubicin, gemcitabine)		
Solitary Fibrous Tumor			
Preferred: • **Pazopanib** • **Sunitinib** • **Sorafenib** • Bevacizumab + temozolomide	*Other recommended:* • Trabectedin • Anthracycline- or gemcitabine-based regimens (eg, with doxorubicin or gemcitabine)		

Abbreviations: dMMR, mismatch repair deficient; IV, intravenous; LMS, leiomyosarcoma; Mb, megabase; MSI-H, high microsatellite instability; mut, mutations; NCCN, National Comprehensive Cancer Network; NSAID(s), nonsteroidal anti-inflammatory drug(s); STS, soft tissue sarcoma; TMB-H, high tumor mutational burden

[a] *Evidence/Consensus Category 1 (C1): recommendation is based upon high-level evidence and a uniform NCCN consensus; Category 2A (C2A): based on lower-level evidence, but with still uniform NCCN consensus; Category 2B (C2B): based on lower-level evidence, and majority consensus.*

7.0 OFF-LABEL USES

Table 22 compiles recommendations in support of off-label use (applicable for Micromedex only) and/or evidence ratings from Micromedex and Lexidrug for recognized off-label uses. **Table 22** also addresses whether the off-label use is among NCCN guideline treatment options for the specified disorder. Notably, NCCN guidelines are frequently updated, so the respective notations are subject to change rapidly. Several of the oral anti-VEGF therapies have at least 1 recognized off-label use among these pharmacy compendia; the documented off-label uses per drug may differ across these databases. There were no off-label uses listed in either database for cabozantinib, fruquintinib, tivozanib or vandetanib.

Additional off-label uses for agents that appear unaccounted for in Micromedex/Lexidrug but that appear to have some supportive evidence[§§] are as follows:

- Axitinib is recommended by the NCCN, in combination with pembrolizumab, for the treatment of alveolar soft part sarcoma (a histologic-specific STS).[26]
- Lenvatinib is recommended by the NCCN for *subsequent* therapy in advanced HCC.[4]
- Cabozantinib, combined with atezolizumab, is being pursued for *first-line* treatment of HCC.[4,9] It has been compared to sorafenib treatment (see Section 8.1).[9]
- Cabozantinib is recommended by the NCCN as second-line or subsequent therapy for recurrent endometrial cancer (EC)[28]
- Regorafenib is recommended by the NCCN for subsequent-line treatment of general STS, or as an option for angiosarcoma (a histologic-specific STS).[26]
- Regorafenib is recommended by the NCCN for recurrent or progressive glioblastoma[64]
- Sorafenib is recommended by the NCCN, as "other recommended therapy", for the treatment of platinum-resistant epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer.[65]
- Pazopanib is recommended by the NCCN, as other recommended therapy, for the treatment of platinum-resistant epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer.[65]
- Pazopanib, sorafenib, and cabozantinib are recommended for prostate cancer[66]
- Sunitinib is NCCN recommended for *neoadjuvant treatment* of SDH-deficient GIST[25]
- Sunitinib is NCCN recommended for *first-line* therapy for SDH-deficient GIST (without KIT or PDGFRA mutations)[25]
- Cabozantinib is NCCN recommended for later-in-line therapy of GIST resistant to imatinib and sunitinib.[25]
- Vandetanib can be considered for RAI-refractory DTC in cases for whom clinical trials and other approved systemic therapies are not available, appropriate, or effective.[24]
- Sorafenib or lenvatinib can also be considered for symptomatic or progressing MTC, if clinical trials and other approved systemic therapies are not available, appropriate, or effective (per NCCN guideline).[24]
- Sunitinib is NCCN recommended for locally unresectable or distant metastasized pheochromocytoma/paraganglioma[44]
- Axitinib combined with toripalimab (versus sunitinib monotherapy) has positive evidence from a phase 3 trial for first-line treatment for advanced renal cell carcinoma[67]

[§§] Agents/indications are listed based on information we came across, sometimes inadvertently, during our review of clinical practice guidelines and literature reviews regarding anti-VEGF therapy.

Table 22. Off-Label Uses of Oral Anti-VEGF Therapies per Pharmacy Compendia

Micromedex[a,68]	Lexidrug[b,69]
Axitinib	
Evidence favors efficacy (Category B) • Metastatic renal cell carcinoma, first-line monotherapy[70] (IIb) ○ NCCN listed option (as "useful in certain circumstances" for clear cell histology renal cell carcinoma)[2]	Thyroid cancer, advanced and differentiated (LOE B) • NCCN listed option after other approved/appropriate options, including enrolling in a clinical trial, have been exhausted[24]
Lenvatinib	
Evidence favors efficacy (Category B) • Endometrial cancer (EC), with *dMMR*, used in combination with pembrolizumab for disease progression following prior chemotherapy (IIa) ○ Not listed as an option for these particular clinical characteristics in the NCCN guideline[28]	None listed
Pazopanib	
Evidence favors efficacy (Category B) • GIST, metastatic or advanced, after failure of imatinib and sunitinib (IIb) ○ NCCN listed option for GIST[25]	Desmoid tumors, progressive (LOE B) • NCCN preferred treatment[26] Thyroid cancer, advanced, differentiated (LOE B) • NCCN listed option after other approved/appropriate options including enrolling in a clinical trial have been exhausted[24]

Abbreviations: dMMR, deficient mismatch repair; GIST, gastrointestinal stromal tumor; LOE, level of evidence; NCCN, National Comprehensive Cancer Network; RCTs, randomized controlled trials; STS, soft tissue sarcoma

[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] Lexidrug 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 22. Off-Label Uses of Oral Anti-VEGF Therapies per Pharmacy Compendia

Micromedex[a,68]	Lexidrug[b,69]
Regorafenib	
Evidence favors efficacy (Category B) • Osteosarcoma, metastatic or advanced, progressive, previously treated (IIb) ○ NCCN listed option[71]	Osteosarcoma, metastatic, progressive recurrent, relapsed, or refractory (LOE, B) • NCCN listed option[71]
Sorafenib	

Evidence favors efficacy (Category B)
• Acute myeloid leukemia, FLT3-ITD mutation-positive, maintenance therapy following allogeneic HSCT (IIa)
  ○ NCCN listed option[72]
• GIST, advanced or metastatic disease, after failing treatment with imatinib and sunitinib (IIb)
  ○ NCCN later-in line option[25]
	Angiosarcoma, recurrent or metastatic (LOE B)
	• NCCN recommended for several histologic-specific forms of STS (eg, angiosarcoma, aggressive desmoid tumors, and solitary fibrous tumor) [26]
	GIST, resistant or refractory (LOE B)
	• NCCN later-in line option[25]

Abbreviations: dMMR, deficient mismatch repair; GIST, gastrointestinal stromal tumor; LOE, level of evidence; NCCN, National Comprehensive Cancer Network; RCTs, randomized controlled trials; STS, soft tissue sarcoma

[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] Lexidrug 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 22. Off-Label Uses of Oral Anti-VEGF Therapies per Pharmacy Compendia

Micromedex[a,68]	**Lexidrug**[b,69]
Sunitinib	
Evidence favors efficacy (Category B) • Thyroid cancer, locally advanced or metastatic, progressive, refractory to radioactive iodine ○ NCCN listed option after all other approved/appropriate options including enrolling in a clinical trial have been exhausted[24]	STS, non-GIST (LOE B) • NCCN recommended for several histologic-specific forms of STS (eg, alveolar soft part sarcoma, and solitary fibrous tumor) [26] Thyroid cancer (LOE B) • NCCN listed option after all other approved/appropriate options including enrolling in a clinical trial have been exhausted[24]

Abbreviations: dMMR, deficient mismatch repair; GIST, gastrointestinal stromal tumor; LOE, level of evidence; NCCN, National Comprehensive Cancer Network; RCTs, randomized controlled trials; STS, soft tissue sarcoma

[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] Lexidrug 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

Following our literature search for direct, head-to-head RCTs, we found comparative studies for oral anti-VEGF therapies in the setting of advanced HCC and RCC. No comparative RCTs were found for other overlapping indicated disease states (ie, GIST, or thyroid cancer).

8.1 Comparative Evidence in the Setting of Advanced Hepatocellular Carcinoma (HCC)

Three of the 4 oral anti-VEGF agents approved for advanced HCC have been included in head-to-head RCTs. Each comparison involved sorafenib (the early long-standing first-line therapy) as the comparator: 2 RCTs (REFLECT/Ding et al) compared lenvatinib to sorafenib, and 1 compared cabozantinib +/- atezolizumab to sorafenib (COSMIC 312)**.** Notably the comparison study with cabozantinib involved its use off-label for first-line systemic therapy (considering its approval is for second-line therapy thus far). Regorafenib, which is approved and guideline recommended for subsequent therapy, has not been compared to other oral anti-VEGFs. No other head-to-head studies with oral agents of interest were found among the SR evidence. This is congruent with the NCCN guideline that also notes a lack of comparative evidence for treatment *after* first-line systemic therapy.[47]

Prior to 2018, sorafenib was the standard-of-care first-line systemic therapy for unresectable HCC.[6,73] Subsequent to the REFLECT RCT that demonstrated non-inferiority of lenvatinib to sorafenib for the primary outcome of overall survival, lenvatinib was approved by the FDA and became an additional NCCN guideline-recommended first-line option for unresectable HCC.[4] Sorafenib remains a recommended first-line option. Other novel combinations are also being explored for first-line therapy, such as cabozantinib + atezolizumab (compared to sorafenib), but the NCCN has yet to include this regimen as a recommended option.[4]

8.1.1 Lenvatinib vs sorafenib for first-line therapy (2 RCTs; FDA-approved dosages)

Four recent SRs (published in 2023) cite an RCT (REFLECT) comparing lenvatinib and sorafenib monotherapies for first-line systemic treatment of unresectable HCC.[7,73-75] REFLECT was an open-label, phase 3, non-inferiority trial comparing lenvatinib 12 mg or 8 mg per day (depending on body weight above/below 60 kg; n= 478) to sorafenib 400 mg twice daily each 28-day cycle (n= 476).[6] The majority (99%) of included patients had Child-Pugh class A liver disease. Non-inferiority of lenvatinib to sorafenib was demonstrated for the primary outcome of median overall survival (OS; 13.6 months versus 12.3 months; hazard ratio [HR] 0.92, 95% CI 0.79, 1.06). Lenvatinib lead to a significant improvement over sorafenib with respect to the secondary outcomes of progression-free survival (PFS; 7.4 versus 3.7 months), and the odds of achieving an objective response. The rate of disease control also appeared better with lenvatinib (76% vs. 61%).[6]

Nonetheless, the risk of adverse events (AEs) grade 3 or higher was greater with lenvatinib treatment versus sorafenib, based on a systematic review meta-analysis estimate for this individual study (relative risk of 1.13; 95% CI 1.04, 1.22).[7] Authors noted that adverse event profiles of lenvatinib were consistent with those previously observed. The most common AEs (of any-grade, in at least 25% of patients)

numerically higher in the lenvatinib vs. sorafenib group were hypertension (42% vs. 30%), decreased appetite (34% vs. 27%), decreased weight (31% vs. 22%), fatigue (30% vs. 25%), and proteinuria (25% vs. 11%). The most common AEs (of any-grade, in at least 25% of patients) numerically higher in the sorafenib vs. lenvatinib group were palmar-plantar erythrodysesthesia (52% vs. 27%), diarrhea (46% vs. 39%), and alopecia (25% vs. 3%).[6]

Three SRs[76-78] (published in 2023) cite a small RCT (Ding et al) in treatment-naive adults with unresectable HCC complicated by portal vein tumor thrombus[***] (PVTT), that compared lenvatinib and sorafenib in combination with arterial directed therapy (ADT).[8] Included patients had a Child-Pugh class of A or B. Patients were randomized to lenvatinib 12 mg or 8 mg per day (depending on body weight above/below 60 kg; n= 32) or sorafenib 400 mg twice daily each 28-day cycle (n= 32), both in combination with transarterial chemoembolization[†††] (TACE, a type of arterial direct therapy). Lenvatinib/TACE outperformed sorafenib/TACE for the primary endpoint of mean time-to-progression (TTP) (4.7 vs 3.1 months; HR 0.55; 95% CI 0.32, 0.95, P = 0.029) and the secondary endpoint of objective response rate (53.1% vs. 25.0%, P = 0.039). AE rates in each arm were mostly comparable: "Overall, there were no significant differences in either grade 1/2 or grade 3/4 AEs between the 2 groups (all P values >.10), except for higher incidences of grade 1/2 ascites (40.6% vs 9.4%) [but that resolved without complication] and grade 1/2 hoarseness (25% vs 0%)," in the lenvatinib/TACE arm compared to sorafenib/TACE (Ding et al, page 3788).[8]

8.1.2 Cabozantinib +/- atezolizumab vs. sorafenib for first-line systemic therapy (1 RCT; off-label combination use of cabozantinib)

Many 2023 SRs show 1 RCT comparing cabozantinib (with or without atezolizumab) to sorafenib in COSMIC 312, as *first-line* systemic therapy for advanced HCC (ie, untreatable by curative or locoregional therapy). [7,50,74,75,79] Notably, this is an off-label use for cabozantinib which is approved for a second-line therapy after failure of sorafenib. COSMIC 312 was a phase 3, open-label study in treatment-naïve (to systemic therapy) adults with advanced HCC with Child-Pugh class A.[9] Its primary objective was to compare the combination regimen of cabozantinib + atezolizumab to sorafenib. Patients were randomized to cabozantinib 40 mg once daily plus IV atezolizumab 1200 mg every 3 weeks (COMBO arm; n=432), sorafenib 400 mg twice daily (n=217), or cabozantinib 60 mg daily (n=188). The *planned* primary endpoints were progression-free survival (PFS; in the intention-to-treat [ITT] population of the first 372 enrolled), and overall survival (OS; ITT of total-enrolled population) in the COMBO vs. sorafenib groups only.

While the COMBO regimen improved PFS, OS was not significantly improved compared to sorafenib:

- With respect to median PFS, the COMBO group outperformed sorafenib at the primary analysis (6.8 vs. 4.2 months; HR 0.63; 99% CI 0.44, 0.91, P=0.0012; median follow-up of 15.8 months)[9] and similarly at the final analysis (6.9 vs. 4.3 months; HR 0.74, [99% CI 0.56, 0.97], median

[***] PVTT occurs in about 44% to 62% of patients with HCC, contributes to poor prognosis with only months of survival without treatment, and is a complication seldom included in clinical trials, thus, rendering optimal treatment elusive.[7]

[†††] TACE is a locoregional therapy catheter-based infusion designed to block the arterial branch of the hepatic artery that supplies the liver cancer (ie, arterially directed therapy). TACE also involves injecting chemotherapy into the branch, thereby providing more localized therapy. For this study TACE components included embosphere microspheres 300-500 mm, lipiodol 5-20 mL, and epirubicin 50 mg.[7]

follow-up 22.1 months).[10] The percentage of patients with 6-month or 12-month PFS in the COMBO vs. sorafenib arms were 55% vs. 40%, and 29% vs. 18%, respectively.[9]

- At the final analysis, the median OS was numerically longer for the COMBO arm (16.5 months) compared to sorafenib (15.5 months); however, the risk was not significantly reduced (HR 0.98 [96% CI 0.78, 1.24], P=0.87).[10]
- At the final analysis, median PFS was non-significantly improved in the cabozantinib-only group (5.8 vs. 4.3 months; HR 0.78 [99% CI 0.56, 1.09].[10] Furthermore, at the earlier analysis, the percentage of patients with an objective response[‡‡‡] appeared similar between cabozantinib and sorafenib (ie, overlapping confidence intervals).[9]

According to SRs, the risk of grade 3 or higher AEs appear higher in the COMBO group vs. sorafenib (event rate 64% vs. 41%; risk ratio 1.39, 95% CI 1.16, 1.69), while rates of total AEs of any grade appeared similar (93% vs. 90%).[7]

8.2 Comparative Evidence in the Setting of Advanced Renal Cell Carcinoma (RCC)

Each oral anti-VEGF approved for advanced RCC has been compared to either to sorafenib or sunitinib, which are the earliest approved agents of the oral anti-VEGF drug-class. There is 1 RCT each for axitinib, pazopanib, sunitinib, or tivozanib *versus sorafenib*; and at least 1 RCT each for axitinib (with avelumab or pembrolizumab), cabozantinib (with or without nivolumab), lenvatinib (with pembrolizumab), and pazopanib *versus sunitinib*. Notably, sorafenib is no longer an NCCN recommended therapy for RCC because it has been superseded by many alternatives. Additionally, sunitinib has been moved from the preferred category to the "other recommended" category for first-line therapy of RCC.

8.2.1 Comparisons vs. Sunitinib

Sunitinib is an older anti-VEGF approved for the treatment of advanced RCC. As a long-standing standard-of-care therapy, many newer anti-VEGF regimens were compared to sunitinib to support their FDA approvals. Based on SRs identified by our literature search, we located trials for the following comparisons:

- Anti-VEGF combination regimens, including axitinib + avelumab, axitinib + pembrolizumab, cabozantinib + nivolumab, and lenvatinib + pembrolizumab, compared to sunitinib in patients with clear cell RCC (ccRCC)
- Anti-VEGF monotherapy, including cabozantinib or pazopanib, versus sunitinib

Because several newer regimens have demonstrated improved outcomes compared to sunitinib, the NCCN now recommends sunitinib as an "other recommended" first-line option for advanced RCC, rather than a preferred therapy. NCCN guideline preferences of therapies have accounted for all the head-to-head trials addressed in this section.

[‡‡‡] Objective response was defined as having a complete or partial radiologic response (per RECIST 1.1, a standardized tool to measure tumor response to treatment) and re-confirmed ≥28 days after initial documentation

8.2.1.1 First-line combination regimens for ccRCC

Many recent SRs[80-89] cite one head-to-head study for each of the following combination regimens versus sunitinib in patients with ccRCC: axitinib + avelumab (Javelin Renal 101, NCT02684006), axitinib + pembrolizumab (Keynote-426, NCT02853331), cabozantinib + nivolumab (CheckMate-9ER, NCT03141177), and lenvatinib + pembrolizumab (CLEAR, NCT02811861). These phase 3 clinical trials supported the FDA-approvals of these regimens for first-line treatment of advanced RCC. Axitinib + pembrolizumab, cabozantinib + nivolumab, and lenvatinib + pembrolizumab are combinations that are NCCN recommended as preferred regimens (category 1) for first-line therapy of ccRCC, whereas axitinib + avelumab is designated as "other recommended" (category 2A) for ccRCC.[2]

8.2.1.1.1 Axitinib + avelumab vs. sunitinib (1 RCT, FDA-approved dosages)

Javelin 101 was an open-label, phase 3 RCT that enrolled therapy-naïve patients (N=886) with advanced ccRCC, regardless of PD-L1 status.[15] Anti-VEGFs were compared at FDA-approved dosages: axitinib 5-10 mg twice daily plus avelumab 10 mg/kg IV every 2 weeks, versus sunitinib 50 mg daily for the first 4 weeks in each 6-week cycle. Co-primary endpoints, OS and PFS, were with respect to patients with PD-L1-positive tumors (N=560, 63% of study population). Secondary key endpoints included OS and PFS in the overall population, and objective response rates.

The combination regimen significantly outperformed sunitinib for PFS in the PD-L1 positive subgroup and in the overall population, however, has not yet demonstrated a significant improvement in OS.[11,15]

- At the first interim analysis, in the PD-L1–positive subgroup, the combination-regimen arm had a significantly longer PFS (13.8 months) vs. the sunitinib arm (7.2 months): HR for disease progression or death, 0.61 (95% CI, 0.47, 0.79; P<0.001; median follow-up of 9.9 and 8.4 months, respectively, per arm). Similarly, a significant benefit in PFS was obtained in the overall population treated with the combination (13.8 months) vs. sunitinib (8.4 months): HR 0.69; 95% CI 0.56, 0.84; P<0.001.[15] At the most recent interim analysis (data cut off April 28, 2020 with median follow-up of about 34 months), the benefit in PFS in the PD-L1–positive subgroup and in the overall population remained significant for the experimental arm vs. sunitinib (HR 0.67; 95% CI 0.57, 0.79, one sided P<0.0001 for the PD-L1 positive subgroup; and HR 0.58; 95% CI 0.47, 0.72, one-sided P < 0.0001 for the overall population).[11]
- While fewer patients in the PD-L1–positive subgroup who were treated with the combination regimen experienced deaths from any cause (13.7% vs. 15.2%), the hazard ratio was not significantly reduced (0.82; P = 0.38).[15] Yet, the OS assessment remained immature at the initial and April 2020 assessment.[11]
- Significantly more patients treated with combination therapy, in the PD-L1 positive subgroup and overall population, had an objective response at the initial and secondary interim assessments; objective response rates ranged from 51% to 59% for combination treatment groups vs. 26% to 32% with sunitinib.[11,15]

At the initial analysis, nearly all patients in each treatment arm experienced an AE of any grade (99.5% vs. 99.3%). Additionally, grade 3 or higher AEs were comparable in each treatment arm (71.2% vs. 71.5%).[15] Fewer proteinuria events occurred in the sunitinib arm, however, the risk ratio was non-significantly reduced.[87]

Although axitinib + avelumab outperformed sunitinib for PFS, the NCCN guideline recommends this combination as an "other recommended" (similar to sunitinib) first-line regimen (category 2A) for patients with ccRCC of any prognostic risk group.[2]

8.2.1.1.2 Axitinib + pembrolizumab vs. sunitinib (1 RCT; FDA-approved dosages)

Keynote-426 was an open-label RCT that enrolled systemic therapy-naïve patients (N=861) with advanced ccRCC, regardless of PD-L1 status.[12] Treatment arms were compared at FDA-approved dosages: axitinib 5-10 mg twice daily plus pembrolizumab 200 mg IV every 3 weeks, versus sunitinib 50 mg daily for the first 4 weeks in each 6-week cycle. The combination regimen significantly outperformed sunitinib for the co-primary endpoints, OS and PFS, at the initial interim analysis with a median follow-up of 12.8 months[12]:

- OS at 12 months in the combination group was 90% compared to 78% in the sunitinib group (HR for death, 0.53; 95% CI 0.38, 0.74; P<0.0001)
- Median PFS in the combination group was 15 months compared to 11 months in the sunitinib group (HR for disease progression or death, 0.69; 95% CI 0.57, 0.84; P<0.001)
- Objective response rate was 59% in the experimental arm vs. 36% with sunitinib (P<0.001 for the difference).

Significant improvements were also observed within subgroups regardless of risk status (favorable, intermediate, and poor risk) or PD-L1 expression status. More patients in the combination arm experienced AEs compared to in the sunitinib arm (52% vs. 36%); however, grade 3 or higher AEs were comparable in each group (76% vs. 71%, respectively).[12] The trend was similar with respect to proteinuria events, with a significantly lower risk of proteinuria events of any grade occurring in the sunitinib arm, but overall, a similar risk of grade 3-5 events in each arm.[87]

Because axitinib + pembrolizumab outperformed sunitinib for PFS and overall response rate, the NCCN guideline recommends this combination as a preferred, first-line regimen option (category 1) for patients with ccRCC of any risk group.[2]

8.2.1.1.3 Cabozantinib + nivolumab vs. sunitinib (1 RCT; FDA-approved dosages)

CheckMate 9ER was an open-label RCT that enrolled systemic therapy-naïve patients (N= 651) with advanced ccRCC, regardless of PD-L1 status.[13] Treatment arms were compared at FDA-approved dosages: cabozantinb 40 mg daily plus nivolumab 240 mg every 2 weeks, and sunitinib 50 mg daily for 4 weeks of each 6-week cycle. Over a median follow-up of 18.1 months, the combination arm had a longer PFS (primary endpoint), greater probability of OS at 12 months, and more patients achieved an objective response, compared to the sunitinib arm[13]:

- Median PFS was 16.6 vs 8.3 months with cabozantinib + nivolumab vs sunitinib, respectfully (HR for disease progression or death, 0.51; 95% CI 0.41, 0.64; P<0.001).
- Probability of OS at 12 months was 85.7% and 75.6% with respect to cabozantinib + nivolumab vs. sunitinib treatment (HR for death, 0.60; 99% CI 0.40, 0.89, P = 0.001).
- Objective response occurred in 55.7% vs. 27.1% (P<0.001 for the difference) of the patients receiving cabozantinib + nivolumab vs. sunitinib, respectfully.

Efficacy benefits with cabozantinib + nivolumab were consistent across subgroups based on PD-L1 status or prognosis risk status.[13] Reported grade 3 or higher AEs occurred in 75.3% vs. 70.6% of cabozantinib + nivolumab- or sunitinib-treated patients, respectively.[13]

Since this combination outperformed sunitinib for several outcomes, the NCCN guideline recommends cabozantinib + nivolumab as a preferred, first-line regimen option (category 1) for patients with ccRCC of any risk group.[2]

8.2.1.1.4 Lenvatinib + pembrolizumab vs. sunitinib (1 RCT; FDA-approved dosages)

CLEAR was an open-label RCT that enrolled systemic therapy-naïve patients (N=1069) with advanced ccRCC, regardless of PD-L1 status.[14] Treatment arms were compared at FDA-approved dosages: lenvatinib 20 mg daily (in a 21-day cycle) plus pembrolizumab 200 mg IV every 3 weeks, versus sunitinib 50 mg daily for the first 4 weeks in each 6-week cycle. This study also included a lenvatinib + everolimus[§§§] combination arm.[14] Lenvatinib + pembrolizumab significantly improved PFS (primary endpoint), OS, and objective response compared to sunitinib:

- In the primary analysis, PFS improved with lenvatinib + pembrolizumab compared to sunitinib (median PFS 23.9 vs. 9.2 months; HR for disease progression or death 0.39; 95% CI 0.32, 0.49).[14] The benefit in PFS was maintained over longer-term follow-up points (data cut-off March 31, 2021, HR 0.42 [95% CI, 0.34, 0.52]; and data cut-off July 31,2022 HR 0.47 [95% CI 0.38, 0.57]).[90,91]
- OS at 24 months improved with lenvatinib + pembrolizumab (79.2% vs. 70.4%) compared to sunitinib (HR for death, 0.66; 95% CI 0.49, 0.88; P = 0.005; data cut-off, August 28, 2020).[14] Following this primary analysis, longer-term follow-up for median OS, 23 months after the primary analysis (data cut-off, July 31, 2022), continued to favor lenvatinib + pembrolizumab (OS hazard ratio: 0.79; 95% CI 0.63, 0.99).[91]
- In the primary analysis, a greater percentage of lenvatinib + pembrolizumab-treated patients experienced an objective response compared to sunitinib (71.0% vs. 36.1%; relative risk 1.97, 95% CI 1.69, 2.29).[14] Moreover, benefits with lenvatinib + pembrolizumab over sunitinib were observed regardless of the presence or absence of baseline lung metastases, bone metastases, or liver metastases; prior nephrectomy; or sarcomatoid features.[92]

Grade 3 or higher AEs were numerically higher in the lenvatinib + pembrolizumab group (82.4%) compared to the sunitinib group (71.8%).[14] Additionally, significantly more proteinuria events of any grade, and of grade 3 to 5, occurred more frequently in the experimental arm compared to sunitinib arm (risk ratio for grade 3-5 events: 2.61, 95% CI 1.28, 5.30).[87]

8.2.1.2 Monotherapy for RCC

Several SRs[80,83,85] cite head-to-head studies between cabozantinib or pazopanib compared to sunitinib. There is one head-to-head RCT each for cabozantinib vs. sunitinib in populations with either ccRCC (CABOSUN, NCT01835158) or non-clear cell RCC (nccRCC; SWOG 150, NCT02761057); and one for

[§§§] In CLEAR, lenvatinib/everolimus did not improve overall survival compared to the control, sunitinib; thus, the combination is not approved for first-line treatment of RCC nor recommended by the NCCN for first-line therapy. Nonetheless the combination is approved for subsequent therapy following treatment failure on an anti-angiogenic agent.

pazopanib vs. sunitinib in patients with ccRCC (COMPARZ, NCT0072094). Monotherapy with cabozantinib is an NCCN preferred first-line therapy option for poor or intermediate risk ccRCC, and is a preferred option for nccRCC; whereas pazopanib is designated as an "other recommended" therapy for ccRCC and nccRCC.[2]

8.2.1.2.1 Cabozantinib vs. sunitinib for ccRCC (1 RCT; FDA-approved dosages)

CABOSUN was an open-label, randomized phase II RCT in treatment-naive patients (N=157) with intermediate- or poor-risk[****] advanced ccRCC.[16] Treatment arms were compared at FDA-approved dosages: cabozantinib 60 mg daily, or sunitinib 50 mg daily over the first 4 weeks of the 6 week cycle. Cabozantinib outperformed sunitinib for the primary outcome of PFS and objective response but not for OS[16]:

- PFS was improved with cabozantinib vs sunitinib (8.2 vs. 5.6 months; adjusted HR for disease progression or death, 0.66; 95% CI 0.46, 0.95; one-sided P = .012).
- Median OS numerically improved with cabozantinib compared with sunitinib (30.3 vs. 21.8 months), however the risk was not significantly reduced: adjusted HR, 0.80 (95% CI, 0.50, 1.26).
- Objective response was 33% (95% CI, 23, 44) versus 12% (95% CI, 5.4, 21) with cabozantinib vs. sunitinib, respectfully.

A comparable percentage of patients experienced AEs of any grade (99% in both groups) and grade 3 or 4 AEs: 67% of patients with cabozantinib and 68% with sunitinib.[16]

Based on these positive efficacy results, the NCCN recommends cabozantinib as a first-line preferred option (category 2A) for poor- and intermediate-risk patients with ccRCC.[2]

8.2.1.2.2 Cabozantinib vs. sunitinib for nccRCC (1 RCT; FDA-approved dosages)

SWOG was an open-label phase II trial in treatment-experienced patients (N=152) with advanced papillary RCC.[17] Enrolled patients were those who failed 1 prior systemic therapy, excluding anti-VEGF or MET-targeted TKIs. Treatment arms of interest were compared at FDA dosages. Cabozantinib-treated patients had a significantly longer PFS (9 months vs. 6 months) and a higher objective response rate (23% vs 4%, P=0.010) than sunitinib-treated patients; yet, OS was similar between treatment groups.

- HR for the composite endpoint of disease progression or death: 0.60 (95% CI 0.37, 0.97, one-sided P=0.019) for cabozantinib vs. sunitinib.
- HR for OS: 0.84 (95% CI 0.47, 1.51) for cabozantinib vs. sunitinib
- Grade 3 or 4 AEs occurred in 69% vs. 74% of sunitinib or cabozantinib-treated patients, respectively.

The NCCN recommends cabozantinib monotherapy as a category 2A, preferred option for patients with nccRCC.

[****] Per International Metastatic Renal Cell Carcinoma Database Consortium criteria for prognostic risk

8.2.1.2.3 Pazopanib vs. sunitinib for ccRCC (1 RCT; FDA-approved dosages)

COMPARZ was a non-inferiority study of pazopanib versus sunitinib in patients (N=1110) with ccRCC without prior systemic treatment.[18] FDA-approved dosages were compared: pazopanib 800 mg daily vs. sunitinib 50 mg daily over the first 4 weeks of the 6 week cycle. The trial demonstrated non-inferiority of pazopanib to sunitinib for the primary endpoint of PFS, although the median PFS was numerically longer with sunitinib. Overall survival was also similar between the treatment arms.[18]

- The median PFS with sunitinib vs. pazopanib was 9.5 months (95% CI, 8.3, 11.1) vs. 8.4 months (95% CI, 8.3, 10.9), respectively (HR for progression of disease or death from any cause, 1.05 [95% CI 0.90, 1.22]).
- The median OS was similar between pazopanib (28.4 months [95% CI 26.2, 35.6]) and sunitinib (29.3 months [95% CI 25.3 to 32.5]; HR for death, 0.91 [95% CI 0.76, 1.08]).
- Objective response rates were higher with pazopanib than with sunitinib (31% vs. 25%, P=0.03).

Regarding AEs, sunitinib-treated patients had notably higher incidence rates of hand–foot syndrome (50% vs. 29%), and thrombocytopenia (78% vs. 41%) compared to those treated with pazopanib. Yet pazopanib-treated patients had notably higher incidence rates of elevated alanine aminotransferase compared to sunitinib (60%, vs. 43%).[18] Based on this trial and positive results of a pivotal placebo-controlled trial for pazopanib, the NCCN recommends pazopanib for first-line therapy of ccRCC across all risk groups (category 2A) as an "other recommended regimen," similar to sunitinb.[2]

8.2.2 Comparaisons vs. Sorafenib

Many 2023 SRs cite comparative RCTs for *first-line* therapy of ccRCC with axitinib, pazopanib or sunitinib, or tivozanib[93] compared to sorafenib.[80,83,85,94] Several SRs also compile comparative studies with axitinib or tivozanib (vs. sorafenib) in the setting of ccRCC *subsequent* therapy after failing previous treatments.[94,95]

8.2.2.1 In the Setting of First-line Treatment (FDA-approved dosages)

In an RCT (SWITCH-2, NCT01613846; N=377) designed to assess sequential therapy, authors reported some results with **pazopanib** 800 mg daily vs. sorafenib 400 mg twice daily first-line therapy prior to switching therapies.[19] First-line therapy with pazopanib (vs. sorafenib) was favored with respect median PFS (9.3 vs. 5.6 months) and overall response rate (non-overlap in confidence intervals). Regarding AEs with the first-line arms of the study, hypertension and nausea were numerically more frequent with pazopanib (and with >10% difference), whereas palmar-plantar erythrodysesthesia syndrome (PPES), rash, and alopecia were numerically more frequent with sorafenib.[19] An SR meta-analysis reported similar safety outcomes between pazopanib and sorafenib in terms of the odds ratio for total AEs, grade 3 or greater events, and treatment discontinuation due to AEs (based on data from SWITCH-2).[85]

In two phase 3, open-label RCTs designed to assess sequential, cross-over therapy, authors reported some results with **sunitinib** (50 mg daily for 4 weeks per each 6 week cycle) vs. sorafenib (400 mg twice daily) as first-line therapy (prior to switching therapies).[20] [21] These were medium size studies with one-to two-hundred patients (SWITCH, NCT00732914; CROSS-J-RCC, NCT01481870). First-line therapy with each treatment resulted in similar outcomes with respect to median PFS (about 9 months with sunitinib vs. 6-7 months with sorafenib; non-significant risk difference), along with similar objective response

rates.[20,21] An SR meta-analysis that included these 2 RCTs reported no significant difference between these agents in terms of the odds ratio for total AEs, grade 3 or greater events, and treatment discontinuation due to AEs (based on data from SWITCH and CROSS).[85]

In a separate SR meta-analysis with a different set of RCTs (5 small RCTs conducted in China), no significant differences were reported between sorafenib and sunitinib regarding the meta-analysis effect estimate for the odds of 2-year PFS, 2-year OS, disease control, and objective response (based on the RCT evidence only).[96]

Axitinib monotherapy (5 mg twice daily), as first-line treatment (off-label use), demonstrated similar outcomes compared to sorafenib (400 mg twice daily) with respect to the primary endpoint of median PFS (10.1 months vs 6.5 months; HR 0.77 [95% CI 0.56, 1.05]).[70] Yet, more patients on axitinib experienced an objective response, assessed by independent review committee, compared to sorafenib (32% vs. 15%; risk ratio 2.21, 95% CI 1.31, 3.75). Any-grade AEs that were numerically more frequent with axitinib (and with an incidence difference ≥10% from sorafenib) included diarrhea, hypertension, weight loss, decreased appetite, dysphonia, hypothyroidism, and upper abdominal pain; whereas, more sorafenib-treated patients experienced dermatologic reactions including palmar-plantar erythrodysesthesia, rash, alopecia, and erythema. Serious AEs were numerically more frequent with axitinib vs. sorafenib (34% vs. 25%).[70]

The NCCN includes axitinib as a first-line option for ccRCC (designated as "useful in certain circumstances"), although this is an off-label use.[2] We are aware of another study[97] assessing off-label use of tivozanib as a first-line therapy for RCC (compared to sorafenib), however, this agent is not recommended for first-line use by the NCCN.

8.2.2.2 Subsequent-line Treatment (FDA-approved dosages)

Several SRs cite comparative studies between **axitinib** 5 mg twice daily (AXIS, NCT00678392; N= 723)[95] or **tivozanib** 1.5 mg daily (TIVO-3, NCT02627963; N=350), compared to sorafenib 400 mg twice daily.[94,95,98] While these studies were open-label with respect to participants and investigators, the radiologic assessments for PFS and objective response rates were conducted by masked radiologists.

Axitinib demonstrated PFS benefit over sorafenib in the AXIS RCT (6.7 vs. 4.7 months) but did not provide a benefit in OS.[23] Similarly, in the TIVO-3 RCT, tivozanib outperformed sorafenib for PFS (5.6 vs. 3.9 months) but did not provide OS benefit .[22] In both studies, significantly more patients achieved an objective response with axitinib or tivozanib vs. sorafenib. In the TIVO-3 study, agents were compared as third- or fourth-line therapy (after failing at least two previous systemic treatments including at least one anti-VEGF agent),[22] while AXIS compared agents as second-line therapy after failing a sunitinib-based regimen. [23]

Axitinib AEs occurring with a greater incidence and with at least a 10% difference than with sorafenib included the following: hypertension, nausea, dysphonia, hypothyroidism, and creatinine elevation; while those more frequent sorafenib were dermatologic events (eg, palmar-plantar erythrodysesthesia, alopecia and rash), hypophosphatemia, and hypocalcemia with sorafenib (statistical significance not evaluated). In TIV0-3, grade 3 treatment-related AEs occurring in numerically more patients (and with a ≥5% difference between treatment groups) were hypertension, with tivozanib, and diarrhea, palmar-

plantar erythrodysesthesia, and rash with sorafenib. Overall, serious treatment-related AEs were similar between tivozanib and sorafenib (11% vs. 10% of patients).[22]

8.3 Notes Regarding SRs for Thyroid Cancer, GIST, and mCRC

Thyroid Cancer: According to recent 3 SRs (published between 2022 to 2024), there are no head-to-head trials available comparing oral anti-VEGF therapies for thyroid cancer.[99-102]

GIST: According to a recent SR[103] (2023) and the NCCN guideline the 2 oral anti-VEGF therapies approved for GIST (sunitinib and regorafenib) have not yet been compared to each other in a head-to-head RCT. These agents are approved for GIST after failure of imatinib (for sunitinib) or after failure of imatinib and sunitinib (for regorafenib). The NCCN guideline also includes them as an option as first-line therapy for scenarios in which the tumor is not likely to respond to imatinib (wild type GIST, SDH-deficient).[25]

mCRC*:* Consistent with the NCCN and ASCO guidelines, which are absent of head-to-head anti-VEGF comparative RCTs, several recent SRs (published between 2021 and 2023) also show that there are no head-to-head studies between fruquintinib and regorafenib, or other oral anti-VEGF therapies.[104-109]

9.0 SAFETY

9.1 Contraindications and Warnings

Of the oral anti-VEGFs, only sorafenib and vandetanib have labeled contraindications. Sorafenib is contraindicated in combination with carboplatin and paclitaxel in patients with squamous cell lung cancer because a higher mortality rate was observed compared to controls with this combination. Sorafenib is also contraindicated in patients with a history of severe hypersensitivity to sorafenib. Vandetanib is contraindicated in patients with congenital long QT syndrome.

Oral anti-VEGF therapies have many warnings in common. As a class, they slow/impair wound healing and are associated with a small, elevated risk for hemorrhage, thromboembolic events, and hypertension. All except 1 or 2 oral anti-VEGF agents (specified below) also have warnings for the following:

- Cardiac failure and/or major adverse cardiac events (MACE): all except cabozantinib
- Posterior reversable encephalopathy syndrome: all except sorafenib
- Hepatotoxicity: all except tivozanib and vandetanib
- Thyroid dysfunction or elevation of thyroid stimulating hormone (TSH): all except regorafenib

In addition to cardiac ischemia- or failure-related warnings, some agents also have the potential to prolong the QTc interval: lenvatinib, pazopanib, sorafenib, sunitinib, and vandetanib. Of the 9 oral anti-VEGFs, at least half have warnings for gastrointestinal perforation, renal failure and/ proteinuria, or dermatologic-related toxicity such as palmar-plantar erythrodysesthesia.

Warnings that are unique to 1 or 2 oral anti-VEGFs include the following:

- Thrombotic microangiopathy: pazopanib, sunitinib
  - Other agents have general warnings for venous and/or arterial thrombotic events
- Interstitial lung disease/pneumonitis: pazopanib, vandetanib
- Hypocalcemia: cabozantinib, lenvatinib
- Tumor lysis syndrome: pazopanib, sunitinib
- Infection: pazopanib, regorafenib
- Ischemic cerebrovascular events: vandetanib
- Adrenal insufficiency: cabozantinib
- Hypoglycemia: sunitinib
- Increased toxicity in developing organs or with other cancer therapies: pazopanib

Table 23 outlines the warnings/precautions labeled for the oral anti-VEGF therapies, with additional elaborations provided after the table for certain warnings.

Table 23. Labeled Warnings for Oral Anti-VEGF Therapies[29-39]

Warning	AXI	CABO	FRUQ	LENV	PAZO	REG	SOR	SUN	TIV	VAND
Impaired Wound Healing	X	X	X	X	X	X	X	X	X	X
Increased Hemorrhage Risk	X	X	X	X	X	X	X	X	X	X
Gastrointestinal Perforation	X	X	X	X	X	X	X			
Fistula	X	X		X	X	X				
Thromboembolic Events	X	X	X	X	X	*X (cardiac infarct)*	*X (CV events/ infarct)*	*X (CV events, including MI; and TMA events)*	X	*X (ischemic CEV events)*
Major Adverse Cardiac Events (MACE)	X			*Has cardiac dysfunction warning*	*Has cardiac dysfunction warning*	X	X	X	X	*Has heart failure warning*
Cardiac Failure/Dysfunction	X			X	X	*Has CV events warning (ischemia/ infarct)*	*Has CV events warning*	X	X	X
Thrombotic Microangiopathy					X			X		
Ischemic Cerebrovascular Events										X
Hypertension	X	X	X	X	X	X	X	X	X	X
QTc Prolongation				X	X		X	X		X
Posterior Reversible Encephalopathy Syndrome[a]	X	X	X	X	X	X		X	X	X *REMS*
Proteinuria	X	X	X	X	X			X	X	
Renal Failure				X						X
Diarrhea		X		X						X
Hepatotoxicity	X	X	X	X	X	X	X	X		

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

[b] *Also known as hand-foot and skin reaction*

Abbreviations: AXI, axitinib; AE, adverse event, CABO, cabozantinib; CEV, cerebrovascular; CV, cardiovascular; FRUQ, fruquintinib; LENV, lenvatinib; PAZO, pazopanib; PPE, palmar-plantar erythrodysesthesia; REG, regorafenib; REMS, Risk Evaluation and Mitigation Strategy; SOR, sorafenib; SUN, sunitinib; TIV, tivozanib; TMA, Thrombotic Microangiopathy; TSH, thyroid stimulating hormone; VAND, vandetanib

Table 23. Labeled Warnings for Oral Anti-VEGF Therapies[29-39]

Warning	AXI	CABO	FRUQ	LENV	PAZO	REG	SOR	SUN	TIV	VAND
Interstitial Lung Disease/Pneumonitis					X					X
Embryo-fetal Toxicity	X	X	X	X	X	X	X	X	X	X
Thyroid dysfunction, primarily hypothyroidism and/or	X	X		X	X	*No warning but hypo-thyroidism occurred in 5-10% of patients*		X	X	X
impaired TSH suppression/elevation of TSH	X			X	X		X			
Adrenal Insufficiency		X								
Hypoglycemia								X		
Hypocalcemia		X		X						
Osteonecrosis of the Jaw		X		X				X		
Tumor Lysis Syndrome					X			X		
Increased Toxicity in Developing Organs					X					
Infection			X		X	X				
Increased Toxicity with Other Cancer Therapies					X					
Dermatologic Toxicity		*Has PPE warning*				X	X	X		X
Palmar-plantar erythrodysesthesia (PPE)[b]	*No warning but PPE is a common AE*	X	X	*No warning but PPE is a common AE*					*No warning but PPE is a common AE*	

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

[b] *Also known as hand-foot and skin reaction*

Abbreviations: AXI, axitinib; AE, adverse event, CABO, cabozantinib; CEV, cerebrovascular; CV, cardiovascular; FRUQ, fruquintinib; LENV, lenvatinib; PAZO, pazopanib; PPE, palmar-plantar erythrodysesthesia; REG, regorafenib; REMS, Risk Evaluation and Mitigation Strategy; SOR, sorafenib; SUN, sunitinib; TIV, tivozanib; TMA, Thrombotic Microangiopathy; TSH, thyroid stimulating hormone; VAND, vandetanib

***Gastrointestinal Perforation**: Monitor for signs and symptoms; use with caution in at risk patients*

- Cases of gastrointestinal (GI) perforation, including death, have been reported with certain oral anti-VEGF therapies (axitinib, cabozantinib, fruquintinib, lenvatinib, pazopanib, and regorafenib). Use with caution in patients with risk factors for GI perforation. Patients should be monitored for signs and symptoms of GI perforation and the drug discontinued in the event of GI perforation.

***Fistula**: Monitor for signs and symptoms; use with caution in at risk patients*

- Cases of fistula development have been reported with certain oral anti-VEGF therapies (axitinib, cabozantinib, lenvatinib, and pazopanib). Use with caution in patients with risk factors. Patients should be monitored for signs and symptoms. Some package inserts advise to discontinue therapy if a fistula develops (regorafenib) and all describe to discontinue therapy upon development of GI perforation. Others advise withholding therapy in the event of grade 2 or 3 fistula and resuming based on clinical judgement; consider discontinuation in the event of grade 3 fistula; and permanently discontinuing therapy with grade 4 fistula.

***Impaired Wound Healing:** Anti-VEGF therapies can slow/impair wound healing.*

- Anti-VEGF therapy should be paused in patients who experience wound healing complications during treatment, until the wound is adequately healed. They should be withheld for a number of days prior to elective surgery (at least 2 days, axitinib; 7 days for lenvatinib and pazopanib; 10 days for sorafenib; 14 days for fruquintinib and regorafenib; 21 days for cabozantinib and sunitinib; 24 days for tivozanib; 1 month for vandetanib) and should be avoided for at least 2 weeks following a major surgery until adequate wound healing is achieved.

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

- Severe or fatal hemorrhagic events have occurred in patients treated with oral anti-VEGF therapies; this is a warning for all anti-VEGFs. Anti-VEGF agents should be used with caution in patients at risk of bleeding and should be avoided in cases of active severe bleeding (eg, grade 3 or 4); treatment may be paused, dose reduced, or discontinued depending on the severity of induced bleeding. Labeling for certain agents also advises against use in patients with a) untreated brain metastasis or recent active GI bleeding (axitinib), (b) recent history of hemoptysis (cabozantinib, vandetanib), or (c) recent history of hemorrhage, hematemesis, or melena (cabozantinib). Labeling for sorafenib advises to treat tracheal, bronchial, and esophageal infiltration with local therapy in patients with DTC, prior to administering sorafenib treatment.

***Thromboembolic Events** (including cerebro- or cardio-vascular ischemic events): All anti-VEGF therapies have a labeled warning for potential risk of thromboembolic and/or ischemic events)*

- Serious, sometimes fatal, arterial thromboembolic events (ATEs) occurred in patients treated with most oral anti-VEGF therapies. Incidences of ATEs in clinical trials were the following: axitinib (2%), cabozantinib (2%), fruquintinib (0.8%), lenvatinib (2-5%), and tivozanib (2%). Clinical trial incidence of cardiac infarct is reported for regorafenib (0.2%) and pazopanib (2%), or cardiac infarct/ischemia for sorafenib (between 1.9% to 2.7%). Cerebrovascular ischemic events are reported for pazopanib (<1%) and vandetanib (1.3%). Myocardial infarction is reported for sunitinib but an incidence rate is not provided in the package insert.

- Serious, sometimes fatal, VTEs occurred in patients treated with certain oral anti-VEGF therapies. Incidences of VTEs in clinical trials were the following: axitinib (3%), cabozantinib (7%), pazopanib (1-5%), and tivozanib (2.4%).
- A distinct warning for thrombotic microangiopathy (TMA) is also labeled for pazopanib and sunitinib; rare but serious events of TMA, including thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome, were reported in clinical trials with these agents

Major Adverse Cardiac Events (MACE) and/or Cardiac Failure/Dysfunction: *Monitor for signs and symptoms*

- To go along with potential ATE events (described above), most agents also have a warning for MACE and/or cardiac failure/dysfunction. The only agents without such warnings are cabozantinib and fruquintinib, however, these agents do have a warning for ATEs.
- Occurrences of heart failure/dysfunction, including death, were reported with certain oral anti-VEGF agents (axitinib, lenvatinib, pazopanib, tivozanib, and vandetanib). Monitor for signs and symptoms of cardiac failure (and for contributing hypertension) during treatment; may require dose reduction, interruption, or permanent discontinuation. Labeling for pazopanib and sunitinib recommends assessing baseline left ventricular ejection fraction, and periodically thereafter, in patients at risk of cardiac dysfunction (eg, previous exposure to anthracyclines).

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

- Hypertension, including hypertensive crisis has been observed in patients treated with all oral anti-VEGF therapies. Blood pressure should be controlled prior to starting treatment. Monitor blood pressure regularly and treat with antihypertensive therapy if needed. Some package inserts provide specific monitoring intervals for blood pressure: monitor after the first week of treatment, then every 2 weeks to month 2, then monthly thereafter (lenvatinib); weekly for 6 weeks, then with every treatment cycle (regorafenib); weekly for the first 6 weeks, then as needed (sorafenib). Withhold anti-VEGF treatment if not medically controlled; may resume once controlled but consider lower dosages per package insert recommended dose adjustments. Discontinue permanently upon a hypertensive crisis or hypertension that cannot be controlled with antihypertensives.

QTc Prolongation*: Monitor for electrolyte abnormalities and signs and symptoms*

- Certain agents carry a warning regarding their potential to prolong the QTc interval: lenvatinib, pazopanib, sorafenib, sunitinib, and vandetanib. Patients should be monitored for electrolyte abnormalities and electrocardiograms at baseline and periodically during treatment as clinically indicated (eg, at risk patients with history of prolongation, congenital long QT syndrome, congestive heart failure or other relevant cardiac disease, bradyarrhythmias, or those taking other QTc prolongating drugs). Electrolyte imbalances should be corrected prior to starting therapy.

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

- With the exception of sorafenib, oral anti-VEGF agents have a warning regarding the potential for PRES. 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 should be discontinued upon a diagnosis of PRES. Package inserts for the following report <1% of treated patients experienced PRES: axitinib, fruquintinib, lenvatinib, regorafenib, sunitinib; otherwise they do not provide the incidence rate.

Proteinuria*: Most oral Anti-VEGF therapies are associated with a small risk for proteinuria*

- Proteinuria is a labeled warning for most oral anti-VEGF therapies: exceptions include regorafenib, sorafenib, and vandetanib (though vandetanib has a warning for renal failure).
- Monitor urine protein at baseline and periodically throughout treatment. Pause therapy in the event of moderate to severe proteinuria (eg, ≥2 grams/24 hours); may resume at a reduced dose once proteinuria normalizes (or is reduced to ≤grade 1 proteinuria, as stated for fruquintinib). Discontinue anti-VEGF therapy in the event of nephrotic syndrome.

Renal Failure*: Labeled warning for lenvatinib and vandetanib*

- Cases of renal failure occurred during lenvatinib and vandetanib treatment. Vandetanib is not recommended for use during severe renal impairment and should be dose-reduced in patients with moderate renal impairment. Lenvatinib should be withheld or discontinued in the event of grade 3 or 4 renal injury.

Hepatotoxicity*: Labeled warning for most oral anti-VEGF therapies*

- Liver enzyme elevations were observed during the use of most oral anti-VEGF agents. With the exceptions of tivozanib and vandetanib, all other oral anti-VEGFs have a labeled warning for possible hepatotoxicity. Grade 3 and 4 liver elevations were more frequent when used in the approved combination regimens (eg, axitinib + avelumab or pembrolizumab; cabozantinib + nivolumab). Some events were noted as fatal for fruquintinib, lenvatinib and regorafenib. Liver enzymes should be monitored at baseline and periodically throughout therapy with more frequent monitoring to be considered when using combination regimens. In the event of grade 3 or 4 hepatotoxicity, corticosteroids may be needed, temporarily withholding anti-VEGF therapy, and/or permanent discontinuation of the anti-VEGF therapy, especially in the event of severe or life-threatening hepatotoxicity.
- Dose reduction is required for axitinib in moderate hepatic impairment; and has not been studied in severe hepatic impairment.
- Labeling for pazopanib recommends the following monitoring intervals for liver enzymes: test at baseline, week 3, 5, 7, and 9; month 3 and 4, and then periodically as clinically indicated. Labeling for regorafenib recommends monitoring enzymes at least every two weeks through month 2, and at least monthly thereafter. Monitoring should be increased to weekly intervals in the event of elevated enzymes.

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 with each oral anti-VEGF agent at exposures below the expected human therapeutic exposure (ie, using recommended dosages).
- 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 week to 4 months after the last dose, depending on the agent).

Thyroid Dysfunction and/or Impairment of Thyroid Stimulating Hormone (TSH) Suppression*: Monitor thyroid function before initiation and periodically during treatment*

- Cases of thyroid dysfunction, primarily manifesting as hypothyroidism, have been reported in clinical trials for most of the oral anti-VEGF agents. For some agents, there is also an elaboration or additional labeled warning in package inserts regarding impaired TSH suppression and/or elevation.

Dermatologic Toxicity or Palmar-plantar Erythrodysesthesia: *Monitor for skin reactions during oral anti-VEGF treatment*

- Most oral anti-VEGFs have warnings regarding dermatologic toxicity and/or palmar-plantar erythrodysesthesia (PPE): cabozantinib, fruquintinib, regorafenib, sorafenib, sunitinib, and vandetanib. Yet, even though some agents do not have a corresponding warning for skin reactions, PPE was a common adverse event in clinical trials for those respective agents. PPE incidence rates documented for any oral anti-VEGF from clinical trials, per package inserts, were as follows: axitinib 33%, cabozantinib 45%, fruquintinib 35%, lenvatinib 32%, regorafenib 53%, sorafenib 69%, sunitinib 14%, and tivozanib 16%. While PPE events are not listed for vandetanib, this agent has a warning for severe skin reactions including toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), and photosensitivity (which can occur during and up to 4 months after treatment discontinuation). Although rare, TEN and/or SJS also occurred with regorafenib, sorafenib, sunitinib.

Interstitial Lung Disease (ILD)/Pneumonitis: *Monitor patients treated with pazopanib or vandetanib for pulmonary symptoms indicative of ILD/pneumonitis*

- Pazopanib and vandetanib have a labeled warning for ILD/pneumonitis. Across clinical trials, ILD/pneumonitis occurred in 0.1% of pazopanib-treated patients; the rate is not reported for vandetanib (in package insert). Patients with ongoing, non-specific respiratory symptoms should be investigated for ILD/pneumonitis.

9.2 Adverse Events

A summary of the most common adverse events (AEs) reported in package inserts are summarized below for oral anti-VEGF therapies, specified according to the disease setting and whether the agent was used in combination with another anti-cancer agent. Management of AEs typically includes dose modification strategies: dose reduction, treatment pause, and/or permanent discontinuation if necessary. A review we are aware of provides management strategies for common AEs including hypertension, proteinuria, diarrhea, fatigue, palmar-plantar erythrodysesthesia syndrome, and decreased appetite that are associated with many of the oral anti-VEGFs.[110]

Axitinib

AEs occurring with an incidence of >20% in treated patients with CRC are listed below according to the treatment regimen. Common AEs occurring across each regimen included *diarrhea, dysphonia, decreased appetite, fatigue, hypertension, nausea, and palmar-plantar erythrodysesthesia.*

- Axitinib monotherapy: diarrhea, hypertension, fatigue, decreased appetite, nausea, dysphonia, palmar-plantar erythrodysesthesia, weight loss, vomiting, asthenia, constipation
- Axitinib + avelumab: diarrhea, fatigue, hypertension, musculoskeletal pain, nausea, mucositis, palmar-plantar erythrodysesthesia, dysphonia, decreased appetite, hypothyroidism, rash, hepatotoxicity, cough, dyspnea, abdominal pain, and headache
- Axitinib + pembrolizumab: diarrhea, fatigue/asthenia, abdominal pain, hypertension, hepatotoxicity, hypothyroidism, decreased appetite, palmar-plantar erythrodysesthesia, nausea, stomatitis/mucosal inflammation, dysphonia, rash, cough, and constipation

Cabozantinib

AEs occurring with an incidence of >20% are listed below according to the treatment regimen. Common AEs occurring across each regimen included *diarrhea, fatigue, hypertension, decreased appetite, and palmar-plantar erythrodysesthesia.*

- Cabozantinib monotherapy: diarrhea, fatigue, PPE, decreased appetite, hypertension, nausea, vomiting, weight decreased, constipation
- Cabozantinib + nivolumab: diarrhea, fatigue, hepatotoxicity, PPE, stomatitis, rash, hypertension, hypothyroidism, musculoskeletal pain, decreased appetite, nausea, dysgeusia, abdominal pain, cough, and upper respiratory tract infection.

Fruquintinib

AEs occurring with an incidence ≥20% in clinical trials for mCRC, as fruquintinib monotherapy, were *hypertension, palmar-plantar erythrodysesthesia, proteinuria, dysphonia, abdominal pain, diarrhea, and asthenia.*

Lenvatinib

AEs occurring with an incidence of >20% or >30% are listed below according to treated indication and treatment regimen. Common AEs occurring in at least 20% across each regimen/indication included *hypertension, fatigue, diarrhea, nausea, abdominal pain, decreased appetite and weight, and proteinuria.*

- For DTC, as lenvatinib monotherapy (incidence >30%): hypertension, fatigue, diarrhea, arthralgia/myalgia, decreased appetite, decreased weight, nausea, stomatitis, headache, vomiting, proteinuria, palmar-plantar erythrodysesthesia syndrome, abdominal pain, and dysphonia
- For HCC, as lenvatinib monotherapy (incidence >20%): hypertension, fatigue, diarrhea, decreased appetite, arthralgia/myalgia, decreased weight, abdominal pain, palmar-plantar erythrodysesthesia syndrome, proteinuria, dysphonia, hemorrhagic events, hypothyroidism, and nausea.
- For RCC, as lenvatinib + pembrolizumab (incidence >20%): fatigue, diarrhea, musculoskeletal pain, hypothyroidism, hypertension, stomatitis, decreased appetite, rash, nausea, decreased weight, dysphonia, proteinuria, palmar-plantar erythrodysesthesia syndrome, abdominal pain, hemorrhagic events, vomiting, constipation, hepatotoxicity, headache, and acute kidney injury,
- For RCC, as lenvatinib + everolimus (incidence >30%): diarrhea, fatigue, arthralgia/myalgia, decreased appetite, vomiting, nausea, stomatitis/oral inflammation, hypertension, peripheral edema, cough, abdominal pain, dyspnea, rash, decreased weight, hemorrhagic events, and proteinuria
- For EC, as lenvatinib + pembrolizumab (incidence >20%): hypertension, fatigue, diarrhea, decreased appetite, arthralgia/myalgia, decreased weight, abdominal pain, palmar-plantar erythrodysesthesia syndrome, proteinuria, dysphonia, hemorrhagic events, hypothyroidism, and nausea.

Pazopanib

AEs occurring with an incidence of >20% are listed below according to the treated indication. Common AEs occurring with each indication were *diarrhea, nausea, vomiting, hypertension, and hair depigmentation.*

- For RCC, as pazopanib monotherapy: diarrhea, hypertension, hair color changes (depigmentation), nausea, anorexia, and vomiting
- For STS, as pazopanib monotherapy: fatigue, diarrhea, nausea, decreased weight, hypertension, decreased appetite, vomiting, tumor pain, hair color changes, musculoskeletal pain, headache, dysgeusia, dyspnea, and skin hypopigmentation.

Regorafenib

AEs occurring with an incidence of >20% included *gastrointestinal and abdominal pain, palmar-plantar erythrodysesthesia, asthenia/fatigue, diarrhea, nausea, decreased appetite and weight, hypertension, infection, dysphonia, hyperbilirubinemia, fever, mucositis, and rash.*

Sorafenib

AEs occurring with an incidence of >20% included *diarrhea, fatigue, infection, alopecia, hand-foot skin reaction, rash, weight loss, decreased appetite, nausea, gastrointestinal and abdominal pains, hypertension, and hemorrhage.*

Sunitinib

AEs occurring with an incidence of >20% included *fatigue/asthenia, diarrhea, mucositis/stomatitis, nausea, decreased appetite/anorexia, vomiting, abdominal pain, hand-foot syndrome, hypertension, bleeding events, dysgeusia/altered taste, dyspepsia, and thrombocytopenia.*

Tivozanib

AEs occurring with an incidence of >20% included *fatigue, hypertension, diarrhea, decreased appetite, nausea, dysphonia, hypothyroidism, cough, and stomatitis.*

Vandetanib

AEs occurring with an incidence of >20% and greater than in the control arm included *diarrhea/colitis, rash, acneiform dermatitis, hypertension, nausea, headache, upper respiratory tract infections, decreased appetite and abdominal pain.*

10.0 DRUG INTERACTIONS

Most of the reviewed oral anti-VEGF agents have the potential for clinically significant drug-drug interactions related to cytochrome (CYP) P450 enzymes, mainly via CYP3A4 (with the exception of lenvatinib). Certain agents (lenvatinib, pazopanib, sorafenib, sunitinib vandetanib) also have warnings regarding their potential to prolong the QTc interval, and therefore, should be avoided in combination with other QT/QTc prolongating drugs. **Table 24** summarizes the drug-drug interactions for the reviewed oral anti-VEGF agents, according to their respective product labeling.

Table 24. Drug-drug Interactions for Oral Anti-VEGF Agents[29-39]

Axitinib	• Avoid combination with strong CYP3A4/5 inducers and inhibitors; reduce dose if combination use with strong CYP3A4/5 *inhibitors* cannot be avoided
Cabozantinib	• Increase dose if combination with strong CYP3A4 *inducers* cannot be avoided • Reduce dose if combination with strong CYP3A4 *inhibitors* cannot be avoided
Fruquintinib	• Avoid combination with strong or moderate CYP3A inducers
Lenvatinib	• Avoid combination with drugs that prolong the QT/QTc interval
Pazopanib	• Avoid in combination with strong CYP3A4 inhibitors; reduce dose if concomitant use with strong CYP3A4 inhibitors cannot be avoided • Avoid in combination with strong CYP3A4 inducers or gastric acid-reducing agents • Avoid in combination with agents that have narrow therapeutic windows and that are metabolized by CYP3A4, CYP2D6, or CYP2C8 • If used with simvastatin, monitor (weekly) for liver enzyme elevations
Regorafenib	• Avoid in combination with strong CYP3A4 inducers or inhibitors • Regorafenib may increase exposure to BCRP substrates (eg, fluvastatin, atorvastatin, methotrexate)
Sorafenib	• Avoid in combination with strong CYP3A inducers, neomycin, and QT/QTc prolongating drugs • Monitor INR during warfarin therapy because sorafenib may increase INR levels and risk of bleeding
Sunitinib	• Consider dose reduction when used with strong CYP3A4 inhibitors if concomitant use cannot be avoided • Consider increasing the dose when used with strong CYP3A4 inducers if concomitant use cannot be avoided
Tivozanib	• Avoid combination with strong CYP3A inducers
Vandetanib	• Avoid combination with strong CYP3A4 inducers or with anti-arrhythmic drugs (eg, amiodarone, sotalol, dofetilide) or other agents that prolong the QT interval (eg, clarithromycin, dolasetron, methadone, moxifloxacin) • Vandetanib increases concentrations of drugs that are transported by OCT2 (eg, metformin) and digoxin, thus, additional monitoring for toxicities or digoxin levels are advised with such combinations

Abbreviations: BCRP, breast cancer resistance protein; CYP, cytochrome; INR, International Normalized Ratio; OCT2, organic cation transporter type 2; VEGF, vascular endothelial growth factor

REFERENCES

1. 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/

2. Motzer R, Jonasch E, Agarwal N, et al. NCCN Guidelines: Kidney Cancer, Version 3.2024 *NCCN Clinical Practice Guidelines in Oncology*. 2024, https://www.nccn.org/guidelines/category_1

3. 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

4. Benson A, D'Angelica M, Abrams T, et al. NCCN Guidelines Hepatocellular Carcinoma Version 1.2024 *NCCN Clinical Practice Guidelines in Oncology*. 2024, Accessed April 15, 2024. Available at https://www.nccn.org/professionals/physician_gls/pdf/hcc.pdf

5. 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

6. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *The Lancet*. 2018;391(10126):1163-1173. doi:https://doi.org/10.1016/S0140-6736(18)30207-1

7. 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

8. Ding X, Sun W, Li W, et al. Transarterial chemoembolization plus lenvatinib versus transarterial chemoembolization plus sorafenib as first-line treatment for hepatocellular carcinoma with portal vein tumor thrombus: A prospective randomized study. *Cancer*. 2021;127(20):3782-3793. doi:10.1002/cncr.33677

9. Kelley RK, Rimassa L, Cheng A-L, et al. Cabozantinib plus atezolizumab versus sorafenib for advanced hepatocellular carcinoma (COSMIC-312): a multicentre, open-label, randomised, phase 3 trial. *The Lancet Oncology*. 2022;23(8):995-1008. doi:https://doi.org/10.1016/S1470-2045(22)00326-6 https://www.sciencedirect.com/science/article/pii/S1470204522003266

10. Yau T, Kaseb A, Cheng A-L, et al. Cabozantinib plus atezolizumab versus sorafenib for advanced hepatocellular carcinoma (COSMIC-312): final results of a randomised phase 3 study. *The Lancet Gastroenterology & Hepatology*. 10.1016/S2468-1253(23)00454-5doi:10.1016/S2468-1253(23)00454-5 Accessed 2024/03/06. Available at https://doi.org/10.1016/S2468-1253(23)00454-5

11. Haanen JBAG, Larkin J, Choueiri TK, et al. Extended follow-up from JAVELIN Renal 101: subgroup analysis of avelumab plus axitinib versus sunitinib by the International Metastatic Renal Cell Carcinoma Database Consortium risk group in patients with advanced renal cell carcinoma. *ESMO Open*. 2023;8(3):101210-101210. doi:10.1016/j.esmoop.2023.101210

12. Rini BI, Plimack ER, Stus V, et al. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. *N Engl J Med*. 2019;380(12):1116-1127. doi:10.1056/NEJMoa1816714

13. Choueiri TK, Powles T, Burotto M, et al. Nivolumab plus Cabozantinib versus Sunitinib for Advanced Renal-Cell Carcinoma. *N Engl J Med*. 2021;384(9):829-841. doi:10.1056/NEJMoa2026982 Accessed 2024/01/12. Available at https://doi.org/10.1056/NEJMoa2026982

14. Motzer R, Alekseev B, Rha SY, et al. Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma. *N Engl J Med*. 2021;384(14):1289-1300. doi:10.1056/NEJMoa2035716

15. Motzer RJ, Penkov K, Haanen J, et al. Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. *N Engl J Med*. 2019;380(12):1103-1115. doi:10.1056/NEJMoa1816047 Accessed 2024/01/11. Available at https://doi.org/10.1056/NEJMoa1816047

16. Choueiri TK, Halabi S, Sanford BL, et al. Cabozantinib Versus Sunitinib As Initial Targeted Therapy for Patients With Metastatic Renal Cell Carcinoma of Poor or Intermediate Risk: The Alliance A031203 CABOSUN Trial. *J Clin Oncol*. 2017;35(6):591-597. doi:10.1200/jco.2016.70.7398

17. Pal SK, Tangen C, Thompson IM, Jr., et al. A comparison of sunitinib with cabozantinib, crizotinib, and savolitinib for treatment of advanced papillary renal cell carcinoma: a randomised, open-label, phase 2 trial. *Lancet*. 2021;397(10275):695-703. doi:10.1016/s0140-6736(21)00152-5

18. Motzer RJ, Hutson TE, Cella D, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. *N Engl J Med*. 2013;369(8):722-731. doi:10.1056/NEJMoa1303989

19. Retz M, Bedke J, Bögemann M, et al. SWITCH II: Phase III randomized, sequential, open-label study to evaluate the efficacy and safety of sorafenib-pazopanib versus pazopanib-sorafenib in the treatment of advanced or metastatic renal cell carcinoma (AUO AN 33/11). *Eur J Cancer*. 2019;107:37-45. doi:10.1016/j.ejca.2018.11.001

20. Eichelberg C, Vervenne WL, De Santis M, et al. SWITCH: A Randomised, Sequential, Open-label Study to Evaluate the Efficacy and Safety of Sorafenib-sunitinib Versus Sunitinib-sorafenib in the Treatment of Metastatic Renal Cell Cancer. *Eur Urol*. 2015;68(5):837-847. doi:10.1016/j.eururo.2015.04.017

21. Tomita Y, Naito S, Sassa N, et al. Sunitinib Versus Sorafenib as Initial Targeted Therapy for mCC-RCC With Favorable/Intermediate Risk: Multicenter Randomized Trial CROSS-J-RCC. *Clin Genitourin Cancer*. 2020;18(4):e374-e385. doi:10.1016/j.clgc.2020.01.001

22. Rini BI, Pal SK, Escudier BJ, et al. Tivozanib versus sorafenib in patients with advanced renal cell carcinoma (TIVO-3): a phase 3, multicentre, randomised, controlled, open-label study. *The Lancet Oncology*. 2020;21(1):95-104. doi:10.1016/S1470-2045(19)30735-1 Accessed 2024/02/02. Available at https://doi.org/10.1016/S1470-2045(19)30735-1

23. Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. *Lancet*. 2011;378(9807):1931-1939. doi:10.1016/s0140-6736(11)61613-9

24. Haddad R, Bischoff L, Agosto S, et al. NCCN Guidelines: Thyroid Carcinoma, Version 2.2024 *National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®)*. 2024, https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1470

25. M. von Mehren, Kane J, Armstrong S, et al. NCCN Guidelines: Gastrointestinal Stromal Tumors, Version 1.2024. *National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®)*. 2024, https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1507

26. Mehren Mv, Kane J, Armstrong S, et al. NCCN Clinical Practice Guidelines in Oncology: Soft Tissue Sarcoma, Version 3.2023. 2023, https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1464

27. NCCN and National Comprehensive Cancer Network Foundation. NCCN Guidelines for Patients: Neuroendocrine Tumors, 2022. 2022, NCCN.org/patients

28. Abu-Rustum N, Yashar C, Arend R, et al. NCCN Clinical Practice Guidelines in Oncology: Uterine Neoplasms, Version 2.2024. 2024, https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1448

29. CABOMETYX (cabozantinib) tablets, for oral use. Package Insert. Exelixis Inc.; September 2023.

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

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

32. LENVIMA (lenvatinib) capsules, for oral use. Package Insert. Eisai Inc.; October 2023.

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

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

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

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

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

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

39. FRUZAQLA (fruquintinib) capsules, for oral use. Package Insert. Takeda Pharmaceuticals U.S.A. I; November 2023.

40. 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

41. 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/

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

43. Benson A, Venook A, Adam M, et al. NCCN Guidelines: Colon Cancer, Version 1.2024. *NCCN Clinical Practice Guidelines in Oncology*. 2024, Accessed November 28, 2023. Available at https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf

44. Bergsland E, Goldner W, Benson A, et al. NCCN Clinical Practice Guidelines in Oncology: Neuroendocrine and Adrenal Tumors, Version 1.2023. 2023, https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1448

45. 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

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

47. 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,

48. 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

49. 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

50. 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

51. 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

52. 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

53. 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

54. Padala SA, Barsouk A, Thandra KC, et al. Epidemiology of Renal Cell Carcinoma. *World J Oncol*. 2020;11(3):79-87. doi:10.14740/wjon1279

55. Rathmell WK, Rumble RB, Van Veldhuizen PJ, et al. Management of Metastatic Clear Cell Renal Cell Carcinoma: ASCO Guideline. *Journal of Clinical Oncology*. 2022;40(25):2957-2995. doi:10.1200/JCO.22.00868 Accessed 2024/02/05. Available at https://doi.org/10.1200/JCO.22.00868

56. Huang D, Zhang J, Zheng X, Gao M. Efficacy and Safety of Lenvatinib in Anaplastic Thyroid Carcinoma: A Meta-Analysis. *Front Endocrinol (Lausanne)*. 2022;13:920857. doi:10.3389/fendo.2022.920857

57. 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

58. 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

59. National Institutes of Health. Cancer Stat Facts: Uterine Cancer. Cancer.gov. 2023. Accessed December 7, 2023. Available at https://seer.cancer.gov/statfacts/html/corp.html

60. Neuroendocrine Tumor of the Pancreas: Statistics. Cancer.Net. 2023. Last Updated March 2023. Accessed December 6, 2023. Available at https://www.cancer.net/cancer-types/neuroendocrine-tumor-pancreas/statistics

61. American Cancer Society Inc. Pancreatic Neuroendocrine Tumor Risk Factors. Cancer.org. Last Updated October 2018. Accessed December 14, 2023. Available at https://www.cancer.org/cancer/types/pancreatic-neuroendocrine-tumor/causes-risks-prevention/risk-factors.html

62. Oncology ASoC. Neuroendocrine Tumor of the Pancreas: Risk Factors. Cancer.net. Last Updated February 2023. Accessed December 14, 2023. Available at https://www.cancer.net/cancer-types/neuroendocrine-tumor-pancreas/risk-factors

63. Del Rivero J, Perez K, Kennedy EB, et al. Systemic Therapy for Tumor Control in Metastatic Well-Differentiated Gastroenteropancreatic Neuroendocrine Tumors: ASCO Guideline. *Journal of Clinical Oncology*. 2023;41(32):5049-5067. doi:10.1200/JCO.23.01529 Accessed 2023/12/06. Available at https://doi.org/10.1200/JCO.23.01529

64. 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®)

65. 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,

66. Gao P, Li T, Zhang K, Luo G. Recent advances in the molecular targeted drugs for prostate cancer. *International Urology and Nephrology*. 2023;55(4):777-789. doi:10.1007/s11255-023-03487-3 https://doi.org/10.1007/s11255-023-03487-3

67. Yan XQ, Ye MJ, Zou Q, et al. Toripalimab plus axitinib versus sunitinib as first-line treatment for advanced renal cell carcinoma: RENOTORCH, a randomized, open-label, phase III study. *Ann Oncol*. 2024;35(2):190-199. doi:10.1016/j.annonc.2023.09.3108

68. Merative. Micromedex DRUGDEX, Drug Monographs, Non-FDA Uses (In-depth Answers). Merative Micromedex.com; 2024.

69. Drug Monographs (Lexi-Drugs): Uses, Off-label. UptoDate Lexidrug; 2024. Accessed February 7, 2024. Available at http://online.lexi.com.

70. Hutson TE, Lesovoy V, Al-Shukri S, et al. Axitinib versus sorafenib as first-line therapy in patients with metastatic renal-cell carcinoma: a randomised open-label phase 3 trial. *Lancet Oncol*. 2013;14(13):1287-1294. doi:10.1016/s1470-2045(13)70465-0

71. Sybil-Biermann J, Hirebe A, Agulnik M, et al. NCCN Guidelines: Bone Cancer, Version 2.2024. *National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®)*. 2024, https://www.nccn.org/professionals/physician_gls/pdf/bone.pdf

72. Pollyea D, Altman J, Assi R, Bachiashvili K, Fathi A, Foran J, Gojo I. NCCN Guidelines: Acute Myeloid Leukemia, Version 2.2024. *National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®)*. 2024, https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf

73. Hu L, Zheng Y, Lin J, Shi X, Wang A. Comparison of the effects of lenvatinib and sorafenib on survival in patients with advanced hepatocellular carcinoma: A systematic review and meta-analysis. *Clinics and research in hepatology and gastroenterology*. 2023;47(1):102061. doi:https://dx.doi.org/10.1016/j.clinre.2022.102061 Accessed 20221205//. Available at http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med23&NEWS=N&AN=36473632

74. 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

75. 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

76. Hu L, Lin J, Shi X, Wang A. Efficacy of transarterial therapy combined with first-line tyrosine kinase inhibitors for unresectable hepatocellular carcinoma: a network meta-analysis. *World J Surg Oncol*. 2023;21(1):208-208. doi:10.1186/s12957-023-03098-3

77. Deng J, Liao Z, Gao J. Efficacy of Transarterial Chemoembolization Combined with Tyrosine Kinase Inhibitors for Hepatocellular Carcinoma Patients with Portal Vein Tumor Thrombus: A Systematic Review and Meta-Analysis. *Curr Oncol*. 2023;30(1):1243-1254. doi:10.3390/curroncol30010096

78. Liu J-N, Li J-J, Yan S, Zhang G-N, Yi P-S. Transarterial chemoembolization combined with lenvatinib versus transarterial chemoembolization combined with sorafenib for unresectable

hepatocellular carcinoma: A systematic review and meta-analysis. *Front Oncol*. 2023;13:1074793-1074793. doi:10.3389/fonc.2023.1074793

79. Rizzo A, Ricci AD, Fanizzi A, Massafra R, De Luca R, Brandi G. Immune-Based Combinations versus Sorafenib as First-Line Treatment for Advanced Hepatocellular Carcinoma: A Meta-Analysis. *Curr Oncol*. 2023;30(1):749-757. doi:10.3390/curroncol30010057

80. Aldin A, Besiroglu B, Adams A, et al. First-line therapy for adults with advanced renal cell carcinoma: a systematic review and network meta-analysis. *Cochrane Database Syst Rev*. 2023;5(5):CD013798-CD013798. doi:10.1002/14651858.CD013798.pub2

81. Bolek H, Yekedüz E, Ürün Y. Combination therapies in patients with favorable risk metastatic renal cell Carcinoma: A Systematic Review and Meta-Analysis. *Cancer Treat Rev*. 2024;122:102667. doi:10.1016/j.ctrv.2023.102667

82. Farrukh M, Ali MA, Naveed M, et al. Efficacy and Safety of Checkpoint Inhibitors in Clear Cell Renal Cell Carcinoma: A Systematic Review of Clinical Trials. *Hematol Oncol Stem Cell Ther*. 2023;16(3):170-185. doi:10.56875/2589-0646.1027

83. Fujiwara Y, Miyashita H, Liaw BC. First-line therapy for elderly patients with advanced renal cell carcinoma in the immuno-oncology era: a network meta-analysis. *Cancer Immunol Immunother*. 2023;72(6):1355-1364. doi:10.1007/s00262-022-03341-y

84. Patel R, Onyechi A, Mohamed MM, Oyenuga M, Sartaj S. Immunotherapy and Antiangiogenic Therapy for the Treatment of Patients With Advanced Renal Cell Carcinoma: A Systematic Review and an Updated Network Meta-Analysis of Phase III Clinical Trials. *Cureus*. 2023;15(5):e38838. doi:10.7759/cureus.38838

85. Krawczyk K, Śladowska K, Holko P, Kawalec P. Comparative safety of tyrosine kinase inhibitors in the treatment of metastatic renal cell carcinoma: a systematic review and network meta-analysis. *Frontiers in pharmacology*. 2023;14doi:10.3389/fphar.2023.1223929

86. Yanagisawa T, Mori K, Matsukawa A, et al. Updated systematic review and network meta-analysis of first-line treatments for metastatic renal cell carcinoma with extended follow-up data. *Cancer Immunol Immunother*. 2024;73(2):38. doi:10.1007/s00262-023-03621-1

87. Tan AJ, Mo DC, Wu K, et al. Nephrotoxicity of immune checkpoint inhibitor combination therapy in patients with advanced renal cell carcinoma: a meta-analysis. *World journal of urology*. 2023;41(6):1563-1571. doi:10.1007/s00345-023-04407-x http://www.epistemonikos.org/documents/db0ccf466c226d08fda7666753354f7f16735357

88. Yanagisawa T, Mori K, Matsukawa A, et al. Updated systematic review and network meta-analysis of first-line treatments for metastatic renal cell carcinoma with extended follow-up data. *Cancer Immunol Immunother*. 2024;73(2):38-38. doi:10.1007/s00262-023-03621-1

89. Eisinger C, Muluneh B. Combined use of pembrolizumab and lenvatinib: A review. *J Oncol Pharm Pract*. 2023;29(6):10781552231178461-10781552231171466. doi:10.1177/10781552231178461

90. Choueiri TK, Eto M, Motzer R, et al. Lenvatinib plus pembrolizumab versus sunitinib as first-line treatment of patients with advanced renal cell carcinoma (CLEAR): extended follow-up from the

phase 3, randomised, open-label study. *Lancet Oncol*. 2023;24(3):228-238. doi:10.1016/s1470-2045(23)00049-9

91. Motzer RJ, Porta C, Eto M, et al. Lenvatinib Plus Pembrolizumab Versus Sunitinib in First-Line Treatment of Advanced Renal Cell Carcinoma: Final Prespecified Overall Survival Analysis of CLEAR, a Phase III Study. *Journal of Clinical Oncology*. 2024, 10.1200/JCO.23.01569:JCO.23.01569. doi:10.1200/JCO.23.01569 Accessed 2024/02/26. Available at https://doi.org/10.1200/JCO.23.01569

92. Grünwald V, Powles T, Eto M, et al. Phase 3 CLEAR study in patients with advanced renal cell carcinoma: outcomes in subgroups for the lenvatinib-plus-pembrolizumab and sunitinib arms. *Front Oncol*. 2023;13:1223282. doi:10.3389/fonc.2023.1223282

93. Passi I, Billowria K, Kumar B, Chawla PA. Tivozanib: A New Hope for Treating Renal Cell Carcinoma. *Anticancer Agents Med Chem*. 2023;23(5):562-570. doi:10.2174/1871520622666220617103126

94. Xie R, Wu J, Shang B, et al. Optimizing targeted drug selection in combination therapy for patients with advanced or metastatic renal cell carcinoma: A systematic review and network meta-analysis of safety. *Cancer Med*. 2023;12(6):7051-7064. doi:10.1002/cam4.5504

95. Obeng-Kusi M, Kreutzfeldt JJ, Estrada-Mendizabal RJ, Choi BM, Abraham I, Recio-Boiles A. Network meta-analysis of second line and beyond treatment options in metastatic clear cell renal cell carcinoma. *Urologic Oncology: Seminars and Original Investigations*. 2024, https://doi.org/10.1016/j.urolonc.2023.12.002doi:https://doi.org/10.1016/j.urolonc.2023.12.002 https://www.sciencedirect.com/science/article/pii/S1078143923004696

96. Li D, Wan S, Li W, Cheng C, Xu L, Gu P. Sorafenib exhibits lower toxicity and comparable efficacy to sunitinib as a first-line treatment for metastatic renal cell carcinoma: A systematic review and meta-analysis. *Medicine (Baltimore)*. 2023;102(36):e34983. doi:10.1097/md.0000000000034983

97. Motzer RJ, Nosov D, Eisen T, et al. Tivozanib Versus Sorafenib As Initial Targeted Therapy for Patients With Metastatic Renal Cell Carcinoma: Results From a Phase III Trial. *Journal of Clinical Oncology*. 2013;31(30):3791-3799. doi:10.1200/JCO.2012.47.4940 Accessed 2024/02/03. Available at https://doi.org/10.1200/JCO.2012.47.4940

98. Albiges L, McGregor BA, Heng DYC, et al. Vascular endothelial growth factor-targeted therapy in patients with renal cell carcinoma pretreated with immune checkpoint inhibitors: A systematic literature review. *Cancer Treat Rev*. 2024;122:102652-102652. doi:10.1016/j.ctrv.2023.102652

99. Su J, Lu J, Zhang J, Wang M, Yan J, Lin S. A meta-analysis of the efficacy and toxicity of tyrosine kinase inhibitors in treating patients with different types of thyroid cancer: how to choose drugs appropriately? *Curr Opin Oncol*. 2023;35(2):132-144. doi:10.1097/CCO.0000000000000924

100. Ji X, Liang W, Lv G, et al. Efficacy and safety of targeted therapeutics for patients with radioiodine-refractory differentiated thyroid cancer: Systematic review and network meta-analysis. *Front Pharmacol*. 2022;13:933648. doi:10.3389/fphar.2022.933648

101. Xian TC, Yang MY, Zhang XL, Wang J, Luo Y. Meta-Analysis of the Efficacy and Safety Evaluation of Vandetanib in the Treatment of Medullary Thyroid Cancer. *Horm Metab Res*. 2024, 10.1055/a-2231-9192doi:10.1055/a-2231-9192

102. Yu J, Liu Z, Su Y, Peng X, Xie Y. Tyrosine kinase inhibitors for radioiodine refractory differentiated thyroid cancer: A systematic review and meta-analysis. *Clin Endocrinol (Oxf)*. 2024;n/a(n/a)doi:https://doi.org/10.1111/cen.15027 Accessed 2024/03/05. Available at https://doi.org/10.1111/cen.15027

103. Hu K, Zhang H, Shu M, Wang X. Efficacy of post-first-line agents for advanced gastrointestinal stromal tumors following imatinib failure: A network meta-analysis. *Cancer Medicine*. 2023;12(11):12187-12197. doi:https://doi.org/10.1002/cam4.5912 Accessed 2023/10/13. Available at https://doi.org/10.1002/cam4.5912

104. 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

105. 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

106. 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

107. 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):5166. doi:10.3390/jcm10215166

108. 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. *Frontiers in oncology*. 2023;13:1269203. doi:10.3389/fonc.2023.1269203 http://www.epistemonikos.org/documents/4842221cc6e4b14482245510972e5400a808c978

109. Xu X, Yu Y, Liu M, Liang L, Liu T. Efficacy and safety of regorafenib and fruquintinib as third-line treatment for colorectal cancer: a narrative review. *Translational cancer research*. 2022;11(1):276-287. doi:https://dx.doi.org/10.21037/tcr-20-3539

110. Jones A, Degregorio P, Sung MW, Ramji Z, Ren M, Baron AD. Characterization and Management of Adverse Reactions in Patients With Unresectable Hepatocellular Carcinoma Treated With Lenvatinib. *J Adv Pract Oncol*. 2023;14(7):598-607. doi:10.6004/jadpro.2023.14.7.4

111. 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

112. Qin S, Xv Z, Chen X, et al. Comparing efficacy and safety of first-line treatment of metastatic renal cell carcinoma: A Bayesian network meta-regression analysis. *Front Oncol*. 2023;13:1072634. doi:10.3389/fonc.2023.1072634

113. Rizzo A, Nuvola G, Palmiotti G, et al. Hypertransaminasemia in metastatic renal cell carcinoma patients receiving immune-based combinations: a meta-analysis. *Immunotherapy*. 2023;15(2):117-126. doi:10.2217/imt-2022-0023

114. Tan AJ, Mo DC, Wu K, et al. Nephrotoxicity of immune checkpoint inhibitor combination therapy in patients with advanced renal cell carcinoma: a meta-analysis. *World J Urol*. 2023;41(6):1563-1571. doi:10.1007/s00345-023-04407-x

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

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

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

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

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

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

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

APPENDIX A: PRODUCT INDICATIONS AND DOSING

Table A1. Oral Anti-VEGF Indications and Dosing[29-39]

Axitinib
Renal cell carcinoma (RCC), advanced • For first-line treatment, in combination with avelumab or pembrolizumab • As monotherapy after failure of 1 prior systemic therapy • 5 mg twice daily is the starting dose in any regimen; may dose reduce or increase based on response and tolerability, up to 10 mg twice daily.
Cabozantinib

Brand Cabometyx
Renal cell carcinoma (RCC), advanced
• For treatment of advanced RCC as monotherapy
  ○ 60 mg once daily
• For first-line treatment in combination with nivolumab
  ○ 40 mg once daily
Hepatocellular carcinoma (HCC)
• For subsequent therapy after previous treatment with sorafenib
  ○ 60 mg once daily
Differentiated thyroid cancer (DTC), locally advanced or metastatic disease, radioactive iodine-refractory or ineligible
• For patients 12 years of age and older with disease progression following prior VEGFR-targeted therapy
  ○ 60 mg once daily; or 40 mg once daily in pediatric patients with BSA less than 1.2 m^2
Brand Cometriq
Metastatic medullary thyroid cancer (MTC), progressive
• 140 mg once daily

[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. Oral Anti-VEGF Indications and Dosing[29-39]

Fruquintinib
Metastatic colorectal cancer (mCRC) • For adults who previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if with RAS wild-type disease, an anti-EGFR therapy as well   ○ 5 mg daily for the first 21 days of each 28-day cycle
Lenvatinib

Differentiated thyroid cancer (DTC)
• For locally recurrent or metastatic, progressive, radioactive iodine-refractory disease
  ○ 24 mg once daily until disease progression or unacceptable toxicity
Renal cell carcinoma (RCC), advanced disease
• For first-line treatment, in combination with pembrolizumab, for adults with advanced disease
  ○ 20 mg once daily
• For subsequent treatment in adults, in combination with everolimus, following previous treatment with 1 prior anti-angiogenic agent
  ○ 18 mg once daily
Hepatocellular carcinoma (HCC), uresectable desease
• For the first-line treatment
  ○ 12 mg once daily for patients 60 kg or greater; or 8 mg once daily for patients less than 60 kg
Endometrial carcinoma (EC), advanced disease not candidate for curative surgery or radiation
• For use in combination with pembrolizumab, for disease that is mismatch repair proficient (pMMR) or not microsatellite instability-high (MSI-H), and that has progressed following prior systemic therapy in any setting
  ○ 20 mg once daily

Pazopanib
Renal cell carcinoma (RCC), advanced • 800 mg once daily

[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. Oral Anti-VEGF Indications and Dosing[29-39]

Pazopanib continued

Soft tissue sarcoma (STS), advanced

- For treatment after prior chemotherapy
  - 800 mg once daily

Regroafenib

Metastatic colorectal cancer (mCRC)

- For later-in-line treatment after previous treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if RAS wild-type, an anti-EGFR therapy
  - 60 mg once daily for the first 21 days of each 28-day cycle; continue until disease progression or unacceptable toxicity

Gastrointestinal stromal tumors (GISTs), locally advanced, unresectable or metastatic

- For patients previously treated with imatinib mesylate and sunitinib malate
  - 60 mg once daily for the first 21 days of each 28-day cycle; continue until disease progression or unacceptable toxicity

Hepatocellular carcinoma (HCC)

- For patients previously treated with sorafenib
  - 60 mg once daily for the first 21 days of each 28-day cycle; continue until disease progression or unacceptable toxicity

Sorafenib

Hepatocellular carcinoma (HCC), unresectable disease

- 400 mg twice daily

Renal cell carcinoma (RCC), advanced

- 400 mg twice daily

Differentiated thyroid carcinoma (DTC), locally recurrent or metastatic, progressive disease refractory to radioactive iodine treatment

- 400 mg twice daily

[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. Oral Anti-VEGF Indications and Dosing[29-39]

Sunitinib

Gastrointestinal stromal tumor (GIST)
• For subsequent treatment in adults after disease progression on or intolerance to imatinib mesylate
  ○ 50 mg orally once daily for the first 4 weeks of each 6-week cycle
Renal cell carcinoma (RCC), advanced
• For adult patients: 50 mg orally once daily for the first 4 weeks of each 6-week cycle
• For adjuvant treatment in adult patients
  ○ 50 mg orally once daily for the first 4 weeks of a 6-week cycle (Schedule 4/2) for a maximum of 9 cycles
Pancreatic neuroendocrine tumors (pNET), well-differentiated, advanced disease
• For adult patients: 37.5 mg orally once daily

Tivozanib

Renal cell carcinoma (RCC), relapsed or refractory advanced
• For adults with previous treatment with two or more prior systemic therapies
  ○ 1.34 mg taken orally once daily for 21 days, followed by 7 days off treatment for a 28-day cycle; continue until disease progression or unacceptable toxicity
  ○ Note that 1.34 mg capsule of tivozanib contains 1.5 mg tivozanib hydrochloride

Vandetanib
Medullary thyroid cancer (MTC), symptomatic or progressive, unresectable locally advanced or metastatic disease • 300 mg once daily

[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 (phases A-C) involved screening the most recently published systematic review (SRs) first, then refining the search to later publication years tailored to certain drugs/indications as needed (per the rationale summarized in Box 1). Phases A-C of the search strategies are described in detail after Box 1.

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

A. SR Search in Epistemonikos
- a. Searched for 2023/24 SRs of the 9 oral anti-VEGF therapies (axitinib OR cabozantinib OR lenvatinib OR regorafenib OR pazopanib OR sorafenib OR sunitinib OR tivozanib OR vandetanib):
  - **96** results on 1/10/2024
- b. To capture SRs for thyroid cancer, added the year 2022 and thyroid cancer terms with the 4 oral anti-VEGF therapies approved for this indication (cabozantinib, lenvatinib, sorafenib, and vandetanib):
  - **8** results (2022-2024)

B. Supplemental SR search in Ovid-Medline
- a. Searched for 2023/24 SRs of the 9 oral anti-VEGFs: uploaded
  - **137** results on 2/2/2024
- b. Searched for SRs for the newly approved agent, fruquintinib:
  - **11** results on 2/10/2024

C. Supplemental RCT searches in Ovid-Medline and Embase
- a. Searched for 2023/24 RCTs of the 9 oral anti-VEGFs:
  - **242** results from Ovid-Medline on 2/10/2024
  - **320** results from Embase on 3/4/2024
  - RCT supplement search based on SRs covering the following search dates:
    - Wu et al searched for RCTs in Dec. 2022, for HCC[75]; Yanagisawa et al searched for RCTs in June 2023, for RCC first-line therapy[86]; Hu et al searched for RCTs to Feb. 2023,[103] for GIST; Su et al searched for RCTs for thyroid cancer, in June 2022, while Xian et al searched specifically for vandetanib RCTs, to March 2023. Gao et al searched for RCTs to May 2023, for mCRC.[108]

Abbreviations: HCC, hepatocellular cancer; GISTs, gastrointestinal stromal tumors; mCRC, metastatic colorectal cancer; RCC, renal cell carcinoma; RCTs, randomized controlled trials; SRs, systematic reviews

A. Epistemonikos Systematic Review Searches

All Drugs (2023-2024 publications; January 10, 2024 Query)

(title:(axitinib OR cabozantinib OR lenvatinib OR regorafenib OR pazopanib OR sorafenib OR sunitinib OR tivozanib OR vandetanib) OR abstract:(axitinib OR cabozantinib OR lenvatinib OR regorafenib OR pazopanib OR sorafenib OR sunitinib OR tivozanib OR vandetanib))

- **96** results

Agents for Thyroid Cancer (2022-2024 publications; January 10, 2024 Query)

(title:(cabozantinib OR lenvatinib OR sorafenib OR vandetanib) OR abstract:(cabozantinib OR lenvatinib OR sorafenib OR vandetanib)) AND (title:(thyroid OR DTC OR MTC) OR abstract:(thyroid OR DTC OR MTC))

- **8** results

B. Ovid-Medline Supplemental SR Searches

Ovid-Medline Systematic Reviews Search: Oral Anti-VEGFs, 2023 Onward

Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to February 01, 2024

#	Searches	Results
1	(axitinib or cabozantinib or lenvatinib or regorafenib or pazopanib or sorafenib or sunitinib or tivozanib or vandetanib).ti,ab.	22678
2	exp Axitinib/ or exp Sorafenib/ or exp Sunitinib/	10528
3	1 or 2	23796
4	limit 3 to yr="2023 -Current"	2429
5	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. or (Medline or Embase or Pubmed or literature-search).ab. or (systematic-review or meta-analysis).pt.	667564
6	4 and 5	**137**

Ovid-Medline Systematic Reviews Search: Fruquintinib

Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to February 09, 2024

#	Searches	Results
1	fruquintinib.ti,ab,kw,kf.	108
2	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. or (Medline or Embase or Pubmed or literature-search).ab. or (systematic-review or meta-analysis).pt.	669216
3	1 and 2	**11**

C. Ovid-Medline and Embase Supplemental RCT Searches

Ovid-Medline RCT Search: All Oral Anti-VEGFs, 2023 Onward

Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to **February 09, 2024**

#	Searches	Results
1	(axitinib or cabozantinib or fruquintinib or lenvatinib or regorafenib or pazopanib or sorafenib or sunitinib or tivozanib or vandetanib).ti,ab.	22808
2	exp Axitinib/ or exp Sorafenib/ or exp Sunitinib/	10549
3	1 or 2	23928
4	((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.)	1453917
5	3 and 4	3606
6	limit 5 to yr="2023 -Current"	**242**

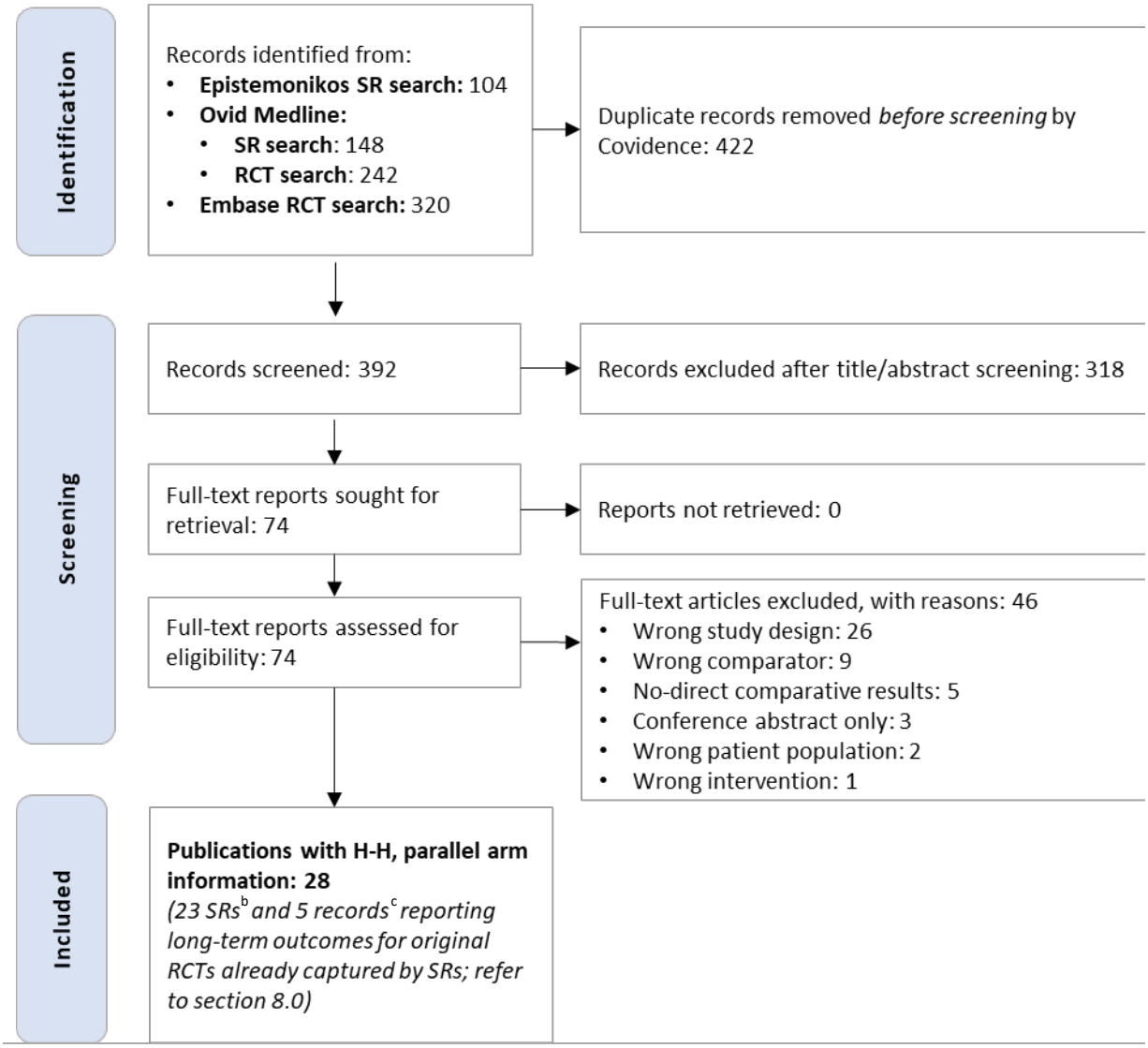
Embase RCT Search: All Anti-VEGFs, 2023 Onward

Query date: 3/4/2024

#1. axitinib:ti,ab OR cabozantinib:ti,ab OR fruquintinib:ti,ab OR lenvatinib:ti,ab OR regorafenib:ti,ab OR pazopanib:ti,ab OR sorafenib:ti,ab OR sunitinib:ti,ab OR tivozanib:ti,ab OR vandetanib:ti,ab	41,967
#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	3,091,981
#3. #1 AND #2	8,552
#4. #3 AND (2023:py OR 2024:py)	560
#5. 'conference abstract'/it OR 'conference review'/it	5,083,326
#6. #4 NOT #5	**320**

APPENDIX C: PUBLICATION SCREENING

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



Abbreviations: ccRCC, clear-cell renal cell carcinoma; H-H, head-to-head; HCC, hepatocellular carcinoma; NMA, network meta-analysis; RCC, renal cell carcinoma; RCT, randomized controlled trial; SRs, systematic reviews;

[a] Modified from Page et al. 2021[111]

[b] SRs in the setting of HCC include (8 SRs): Ciliberto et al[74], Deng et al[77], Fulgenzi et al[7], Hu et al[76], Hu et al[73], Liu et al[78], Meyers et al[50], Rizzo et al[79]

SRs in the setting of RCC include (15 SRs): Alibiges et al[98], Aldin et al[80], Bolek et al[81], Eisinger et al[89], Farrukh et al[82], Fujiwara et al[83], Krawczyk et al[85], Li et al[96], Passi et al[93], Patel et al[84], Qin et al[112], Rizzo et al[113], Tan et al[114], Obeng-Kusi et al[95], Yanagisawa et al[88]

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

Other SRs were identified that searched for H-H studies but that did not find relevant comparisons in the setting of thyroid carcinoma or gastrointestinal stromal tumors; these are not counted in the included number; refer to Section 8.3 for citations.

[c] While the primary RCT publication was already identified from SRs, additional publications for long-term follow-up results or post-hoc analysis was found for the following RCTs:

- *COSMIC 312 (1 additional publication for this trial in HCC of cabozantinib/atezolizumab vs sorafenib; Yau et al[10])*
- *CLEAR (3 additional publications for this trial in ccRCC for lenvatinib/pembrolizumab vs. sunitinib: Choueiri et al[90], Motzer et al[91], and Grunwald et al[92]);*
- *JAVELIN RENAL-101(1 additional publication for this trial in RCC of axitinib/avelumab vs. sunitinib; Haanen et al[11])*

APPENDIX D: EXCLUDED STUDIES

Wrong Study Design

Acitelli E, Maiorca C, Grani G, Maranghi M. Metabolic adverse events of multitarget kinase inhibitors: a systematic review. Endocrine. 2023, 10.1007/s12020-023-03362-2doi:10.1007/s12020-023-03362-2

Beckermann KE, Asnis-Alibozek AG, Atkins MB, et al. Long-Term Survival in Patients With Relapsed/Refractory Advanced Renal Cell Carcinoma Treated With Tivozanib: Analysis of the Phase III TIVO-3 Trial. The oncologist. 2024

Bottinor WJ, Flamand Y, Haas NB, et al. Cardiovascular Implications of Vascular Endothelial Growth Factor Inhibition Among Adolescents/Young Adults in ECOG-ACRIN E2805. Journal of the National Comprehensive Cancer Network : JNCCN. 2023;21(7):725-731.e721. doi:https://dx.doi.org/10.6004/jnccn.2023.7018

Chen J, Wang J, Lin H, Peng Y. Comparison of Regorafenib, Fruquintinib, and TAS-102 in Previously Treated Patients with Metastatic Colorectal Cancer: A Systematic Review and Network Meta-Analysis of Five Clinical Trials. Medical science monitor : international medical journal of experimental and clinical research. 2019;25(dxw, 9609063):9179-9191. doi:https://dx.doi.org/10.12659/MSM.918411

Chen Y-C, Chen J-H, Hsieh F-I. Major adverse cardiovascular events of vascular endothelial growth factor tyrosine kinase inhibitors among patients with different malignancy: A systemic review and network meta-analysis. Journal of the Chinese Medical Association : JCMA. 2024;87(1):48-57. doi:https://dx.doi.org/10.1097/JCMA.0000000000001026

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
http://www.epistemonikos.org/documents/218bd30c99b117f4d222dd9482de3d3e746ea990

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. Frontiers in oncology. 2023;13:1269203. doi:10.3389/fonc.2023.1269203
http://www.epistemonikos.org/documents/4842221cc6e4b14482245510972e5400a808c978

Grunwald V, Ivanyi P, Zschabitz S, et al. Nivolumab Switch Maintenance Therapy After Tyrosine Kinase Inhibitor Induction in Metastatic Renal Cell Carcinoma: A Randomized Clinical Trial by the Interdisciplinary Working Group on Renal Tumors of the German Cancer Society (NIVOSWITCH; AIO-NZK-0116ass. European urology. 2023;84(6):571-578. doi:https://dx.doi.org/10.1016/j.eururo.2023.09.004

Grunwald V, Powles T, Kopyltsov E, et al. Survival by Depth of Response and Efficacy by International Metastatic Renal Cell Carcinoma Database Consortium Subgroup with Lenvatinib Plus Pembrolizumab Versus Sunitinib in Advanced Renal Cell Carcinoma: Analysis of the Phase 3 Randomized CLEAR Study. European urology oncology. 2023;6(4):437-446. doi:https://dx.doi.org/10.1016/j.euo.2023.01.010

Hua X, Yin Z, Liang J, Chen W, Gong H. Efficacy and safety comparison between Lenvatinib and Sorafenib in hepatocellular carcinoma treatment: a systematic review and meta-analysis of real-world study. European journal of gastroenterology & hepatology. 2024;36(1):120-128. doi:https://dx.doi.org/10.1097/MEG.0000000000002668

Jaiswal V, Hameed M, Naz S, et al. Efficacy of lenvatinib versus sorafenib in the primary treatment of advanced hepatocellular carcinoma: A meta-analysis. JGH open : an open access journal of gastroenterology and hepatology. 2023;7(12):832-840. doi:https://dx.doi.org/10.1002/jgh3.12999

Ji X, Liang W, Lv G, et al. Efficacy and safety of targeted therapeutics for patients with radioiodine-refractory differentiated thyroid cancer: Systematic review and network meta-analysis. Frontiers in pharmacology. 2022;13:933648. doi:10.3389/fphar.2022.933648 http://www.epistemonikos.org/documents/71b389ec20d99010c2b2a8119b792b724409154f

Jones A, Degregorio P, Sung MW, Ramji Z, Ren M, Baron AD. Characterization and Management of Adverse Reactions in Patients With Unresectable Hepatocellular Carcinoma Treated With Lenvatinib. Journal of the advanced practitioner in oncology. 2023;14(7):598-607. doi:https://dx.doi.org/10.6004/jadpro.2023.14.7.4

Kudo M, Finn RS, Qin S, et al. Overall survival and objective response in advanced unresectable hepatocellular carcinoma: A subanalysis of the REFLECT study. Journal of hepatology. 2023;78(1):133-141. doi:https://dx.doi.org/10.1016/j.jhep.2022.09.006

Larkin J, Oya M, Martignoni M, et al. Avelumab Plus Axitinib as First-Line Therapy for Advanced Renal Cell Carcinoma: Long-Term Results from the JAVELIN Renal 100 Phase Ib Trial. The oncologist. 2023;28(4):333-340. doi:https://dx.doi.org/10.1093/oncolo/oyac243

Long J, Chen B, Liu Z. Comparative efficacy and safety of molecular targeted agents combined with transarterial chemoembolization in the treatment of unresectable hepatocellular carcinoma: a network meta-analysis. Frontiers in oncology. 2023;13:1179431. doi:10.3389/fonc.2023.1179431 http://www.epistemonikos.org/documents/f8f1cbb9177923b1a63355c98ada3bad8b4d8ac1

McGregor B, Geynisman DM, Burotto M, et al. A Matching-adjusted Indirect Comparison of Nivolumab Plus Cabozantinib Versus Pembrolizumab Plus Axitinib in Patients with Advanced Renal Cell Carcinoma. European Urology Oncology. 2023;6(3):339-348. doi:10.1016/j.euo.2023.01.012 https://www.embase.com/search/results?subaction=viewrecord&id=L2023027358&from=export

Motzer R, George S, Merchan JR, et al. Characterization and Management of Adverse Reactions From the CLEAR Study in Advanced Renal Cell Carcinoma Treated With Lenvatinib Plus Pembrolizumab. Oncologist. 2023;28(6):501-509. doi:10.1093/oncolo/oyac269 https://www.embase.com/search/results?subaction=viewrecord&id=L2025161800&from=export

Raeber ME, Sahin D, Karakus U, Boyman O. A systematic review of interleukin-2-based immunotherapies in clinical trials for cancer and autoimmune diseases. EBioMedicine. 2023;90:104539. doi:10.1016/j.ebiom.2023.104539 http://www.epistemonikos.org/documents/e131c51fb6859140ba1fd26a2967057860195454

Sakellakis M, Zakopoulou R. Current Status of Tivozanib in the Treatment of Patients With Advanced Renal Cell Carcinoma. Cureus. 2023;15(3):e35675. doi:https://dx.doi.org/10.7759/cureus.35675

Tarpgaard LS, Winther SB, Pfeiffer P. Treatment Options in Late-Line Colorectal Cancer: Lessons Learned from Recent Randomized Studies. Cancers. 2023;16(1)doi:https://dx.doi.org/10.3390/cancers16010126

Tomita Y, Motzer RJ, Choueiri TK, et al. Efficacy of avelumab plus axitinib versus sunitinib by numbers of IMDC risk factors and target tumor sites at baseline in advanced renal cell carcinoma: long-term follow-up results from JAVELIN Renal 101. ESMO Open. 2023;8(6)doi:10.1016/j.esmoop.2023.102034 https://www.embase.com/search/results?subaction=viewrecord&id=L2027912640&from=export

Wu D, Jia B, Jia M, 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;13:1274754. doi:10.3389/fonc.2023.1274754 http://www.epistemonikos.org/documents/51f70f8b2017d3e95b8c54a73ac0bcbc520a45d1

Xie R, Wu J, Shang B, et al. Optimizing targeted drug selection in combination therapy for patients with advanced or metastatic renal cell carcinoma: A systematic review and network meta-analysis of safety. Cancer medicine. 2023;12(6):7051-7064. doi:10.1002/cam4.5504 http://www.epistemonikos.org/documents/c850293b6aca4f9bfb172b672766eec6a56ec940

Yanagisawa T, Quhal F, Kawada T, et al. Association between age and efficacy of first-line immunotherapy-based combination therapies for mRCC: a meta-analysis. Immunotherapy. 2023;15(15):1309-1322. doi:10.2217/imt-2023-0039 http://www.epistemonikos.org/documents/c167a7f6ebd0103c3e6b7555b11b3739d7cd7f30

Ye Y, Wang Y, Xu H, Yi F. Network meta-analysis of adjuvant treatments for patients with hepatocellular carcinoma after curative resection. BMC gastroenterology. 2023;23(1):320. doi:10.1186/s12876-023-02955-5 http://www.epistemonikos.org/documents/75d9df9892674b8e08520db999cddb479c503a34

Wrong Comparator (or no direct-comparative results for SRs)

Cao M, Zhou M, Zhang J. Comparison of efficacy and safety for patients with beyond second line treated metastatic colorectal cancer: a network meta-analysis of randomized controlled trials. Journal of chemotherapy (Florence, Italy). 2020;32(4):163-170. doi:https://dx.doi.org/10.1080/1120009X.2020.1728860

Chen J-J, Jin Z-C, Luo B, Wang Y-Q, Li R, Zhu H-D, Teng G-J. New First-line Immunotherapy-based Therapies for Unresectable Hepatocellular Carcinoma: A Living Network Meta-analysis. Journal of clinical and translational hepatology. 2024;12(1):15-24. doi:https://dx.doi.org/10.14218/JCTH.2023.00188

Feng X, Feng G-Y, Tao J, Ao Y-P, Wu X-H, Qi S-G, Shi Z-R. Comparison of different adjuvant therapy regimen efficacies in patients with high risk of recurrence after radical resection of hepatocellular carcinoma. Journal of cancer research and clinical oncology. 2023;149(12):10505-10518. doi:https://dx.doi.org/10.1007/s00432-023-04874-0

Gao Z, Cao C, Bao Y, Fan Y, Chen G, Fu P. Systematic Review and Meta-Analysis of Multitargeted Tyrosine Kinase Inhibitors in Patients With Intractable Metastatic Colorectal Cancer. Technology in cancer

research & treatment. 2020;19(101140941):1533033820943241. doi:https://dx.doi.org/10.1177/1533033820943241

Hu K, Zhang H, Shu M, Wang X. Efficacy of post-first-line agents for advanced gastrointestinal stromal tumors following imatinib failure: A network meta-analysis. Cancer medicine. 2023;12(11):12187-12197. doi:10.1002/cam4.5912 http://www.epistemonikos.org/documents/2e1a6d0eaca421cb1c861b89da4a656c788f209e

Jing Z, Rui Z, Binglan Z. A comparison of regorafenib and fruquintinib for metastatic colorectal cancer: a systematic review and network meta-analysis. Journal of cancer research and clinical oncology. 2019;145(9):2313-2323. doi:https://dx.doi.org/10.1007/s00432-019-02964-6

Li P, Hu M, Liu M, et al. The efficacy and safety of different systemic combination therapies on advanced hepatocellular carcinoma: a systematic review and meta-analysis. Frontiers in oncology. 2023;13:1197782. doi:10.3389/fonc.2023.1197782 http://www.epistemonikos.org/documents/149266cd45f0f48dca2c80678592314c6cf3e558

Su J, Lu J, Zhang J, Wang M, Yan J, Lin S. A meta-analysis of the efficacy and toxicity of tyrosine kinase inhibitors in treating patients with different types of thyroid cancer: how to choose drugs appropriately? Current opinion in oncology. 2023;35(2):132-144. doi:10.1097/CCO.0000000000000924 http://www.epistemonikos.org/documents/db5e9a4615bb142c322b17157c85dd5a47a8dfba

Wu Y, Fan Y, Dong D, et al. Efficacy and safety of regorafenib as beyond second-line therapy in patients with metastatic colorectal cancer: an adjusted indirect meta-analysis and systematic review. Therapeutic advances in medical oncology. 2020;12(101510808):1758835920940932. doi:https://dx.doi.org/10.1177/1758835920940932

Xian T-C, Yang M-Y, Zhang X-L, Wang J, Luo Y. Meta-Analysis of the Efficacy and Safety Evaluation of Vandetanib in the Treatment of Medullary Thyroid Cancer. Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme. 2024, https://dx.doi.org/10.1055/a-2231-9192(gbd, 0177722)doi:https://dx.doi.org/10.1055/a-2231-9192

Xu X, Yu Y, Liu M, Liang L, Liu T. Efficacy and safety of regorafenib and fruquintinib as third-line treatment for colorectal cancer: a narrative review. Translational cancer research. 2022;11(1):276-287. doi:https://dx.doi.org/10.21037/tcr-20-3539

Yu J, Liu Z, Su Y, Peng X, Xie Y. Tyrosine kinase inhibitors for radioiodine refractory differentiated thyroid cancer: A systematic review and meta-analysis. Clinical Endocrinology. 2024, 10.1111/cen.15027((Yu J.; Xie Y., xie.yuping@163.com) Department of oncology, West China School of Public Health and West China Fourth Hospital, Sichuan University, Chengdu, China(Liu Z.; Peng X.) Department of Biotherapy, Cancer Center, West China Hospital, Sichuan Univer)doi:10.1111/cen.15027 https://www.embase.com/search/results?subaction=viewrecord&id=L2028528654&from=export

Zago E, Galluzzo A, Pradella S, Antonuzzo L, Maggi M, Petrone L, Sparano C. Cabozantinib for different endocrine tumours: killing two birds with one stone. A systematic review of the literature. Endocrine. 2024;83(1):26-40. doi:https://dx.doi.org/10.1007/s12020-023-03526-0

Zhang Q, Wang Q, Wang X, Li J, Shen L, Peng Z. Regorafenib, TAS-102, or fruquintinib for metastatic colorectal cancer: any difference in randomized trials? International journal of colorectal disease. 2020;35(2):295-306. doi:https://dx.doi.org/10.1007/s00384-019-03477-x

Conference Abstract Only

Anonymous. Erratum: Nivolumab Plus Cabozantinib vs Sunitinib for First-Line Treatment of Advanced Renal Cell Carcinoma (aRCC): 3-Year Follow-Up From the Phase 3 CheckMate 9 ER Trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2023;41(21):3767. doi:https://dx.doi.org/10.1200/JCO.23.00901

Plimack ER, Powles T, Stus V, et al. Pembrolizumab Plus Axitinib Versus Sunitinib as First-line Treatment of Advanced Renal Cell Carcinoma: 43-month Follow-up of the Phase 3 KEYNOTE-426 Study. European urology. 2023;84(5):449-454. doi:https://dx.doi.org/10.1016/j.eururo.2023.06.006

Rini BI, Plimack ER, Stus V, et al. Pembrolizumab plus axitinib versus sunitinib as first-line therapy for advanced clear cell renal cell carcinoma: 5-year analysis of KEYNOTE-426. 2023;41(17)http://www.epistemonikos.org/documents/5bfc3fb22672aff11353a9a178169c82070c75d5

Wrong Patient Population

Arunachalam A, Zhang I, Zhao B, Frederickson AM, Catherine Pietanza M. Efficacy and safety of treatments for advanced thymic carcinoma after failure of first-line platinum-based chemotherapy: A systematic literature review and meta-analysis. Lung cancer (Amsterdam, Netherlands). 2023;176:132-139. doi:10.1016/j.lungcan.2023.01.003
http://www.epistemonikos.org/documents/0f89a18820bc7a28232d56514bee119ad402e33a

Zhang Z, Zhao Y, Lu F, et al. Multi-targeted tyrosine kinase inhibitors as third-line regimen in advanced non-small cell lung cancer: a network meta-analysis. Annals of translational medicine. 2019;7(18):452. doi:https://dx.doi.org/10.21037/atm.2019.08.51

Wrong Intervention

Yan XQ, Ye MJ, Zou Q, et al. Toripalimab plus axitinib versus sunitinib as first-line treatment for advanced renal cell carcinoma: RENOTORCH, a randomized, open-label, phase III study. Annals of oncology : official journal of the European Society for Medical Oncology. 2024;35(2):190-199. doi:https://dx.doi.org/10.1016/j.annonc.2023.09.3108

APPENDIX E: INTRAVENOUS ANTI-VEGF PRODUCTS BY INDICATED DISEASE STATE

Table E1, lists the intravenous (IV) anti-VEGF therapies available in the US. These agents have 3 indicated disease states in common with oral anti-VEGFs: mCRC, HCC, and RCC. In addition, IV anti-VEGFs have 5 unique indication areas for which the oral anti-VEGF agents are not approved: cervical cancer; gastric or esophagogastric cancer; glioblastoma; NSCLC; and epithelial, ovarian, fallopian tube, or primary peritoneal cancer.

Table E1. IV Anti-VEGF Products by Indicated Disease State[115-121]

IV Anti-VEGFs	Overlapping Disease States with Oral Anti-VEGFs			Disease States Unique to Approved Indications of IV Anti-VEGFs				
	Metastatic colorectal cancer (mCRC)	**Hepatocellular carcinoma, advanced**	**Renal cell carcinoma (RCC), metastatic**	**Cervical cancer**	**Gastric or esophagogastric cancer, advanced or metastatic**	**Glioblastoma, recurrent**	**Non-small cell lung cancer (NSCLC), advanced**	**Epithelial ovarian, fallopian tube, or primary peritoneal cancer**
Bevacizumab (Avastin) ***Bevacizumab Biosimilars*** Mvasi (bevacizumab-awwb) Vegzelma (bevacizumab-adcd) Zirabev(bevacizumab-bvzr) Alymsys (bevacizumab-maly)	X	X (first-line therapy) *Biosimilars do not have this approved indication*	X	X		X	X (for non-squamous histology only)	X[a]
Ramucirumab (Cyramza)	X (for progression after bevacizumab)	X (for cases with prior sorafenib treatment and AFP≥400)			X (for progression after a fluoropyrimidine or platinum regimen)		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] *Alymsys does not have the full span of indicated patients for the respective cancer compared to the originator and other biosimilars of bevacizumab*

Table E2. Approved Disease Areas in Common Between Oral and IV Anti-VEGF Agents[29-39,115-121]

Disease and Agent Approved	Indicated Clinical Scenario
Colorectal cancer, metastatic (mCRC)	
Fruquintinib (PO)	For adults previously treated with an oxaliplatin-, irinotecan-, and fluoropyrimidine-based regimen, an anti-VEGF therapy, and, if RAS wild-type disease, an anti-EGFR therapy; used as monotherapy
Regorafenib (PO)	For patients previously treated with an oxaliplatin-, irinotecan-, and fluoropyrimidine-based regimen, an anti-VEGF therapy, and, if RAS wild-type disease, 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 or irinotecan) 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
Lenvatinib (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 • 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 • For treatment of advanced RCC, as monotherapy
Levatinib (PO)	• For first-line treatment of adults with advanced RCC, in combination pembrolizumab • 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 • 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: EGFR, epidermal growth factor receptor; FOLFIR, fluorouracil, leucovorin, irinotecan; HCC, hepatocellular carcinoma; IV, intravenous; PO, oral; RCC, renal cell carcinoma