



Oncology Oral, Renal Cell Carcinoma Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

| Drug | Manufacturer | Indication(s) |
|---|-------------------|--|
| axitinib (Inlyta®) ¹ | Pfizer | <ul style="list-style-type: none"> Treatment of advanced renal cell carcinoma (RCC) in adults after failure of 1 prior systemic therapy In combination with avelumab for the first-line treatment of advanced RCC In combination with pembrolizumab for the first-line treatment of advanced RCC |
| cabozantinib* (Cabometyx®) ² | Exelixis | <ul style="list-style-type: none"> Treatment of advanced RCC Treatment of hepatocellular carcinoma (HCC) after previous treatment with sorafenib In combination with nivolumab for the first-line treatment of advanced RCC |
| everolimus† (Afinitor®) ³ | generic, Novartis | <ul style="list-style-type: none"> Adults with advanced RCC after failure of treatment with sunitinib or sorafenib Pediatric and adult patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) that requires therapeutic intervention but cannot be curatively resected Adults with progressive neuroendocrine tumors (PNET) of pancreatic origin that are unresectable, locally advanced, or metastatic and adults with progressive, well-differentiated, non-functional neuroendocrine tumors (NET) of gastrointestinal (GI) or lung origin that are unresectable, locally advanced, or metastatic Adults with renal angiomyolipoma and TSC, not requiring immediate surgery Postmenopausal women with advanced hormone receptor (HR)-positive, HER2-negative breast cancer in combination with exemestane after failure of treatment with letrozole or anastrozole |
| everolimus‡ (Afinitor Disperz®) ⁴ | Novartis | <ul style="list-style-type: none"> Adult and pediatric patients with SEGA associated with TSC requiring therapeutic intervention but cannot be curatively resected Adjunctive treatment of patients aged 2 years and older with TSC associated partial-onset seizures |
| lenvatinib (Lenvima®) ⁵ | Eisai | <ul style="list-style-type: none"> In combination with everolimus for patients with advanced RCC following 1 prior anti-angiogenic therapy Treatment of differentiated thyroid cancer (DTC) in patients with locally recurrent or metastatic, progressive radioactive iodine-refractory DTC First-line treatment of unresectable hepatocellular carcinoma (HCC) In combination with pembrolizumab for patients with advanced endometrial carcinoma (EC) that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation |
| pazopanib§ (Votrient®) ⁶ | Novartis | <ul style="list-style-type: none"> Treatment of advanced RCC Advanced soft tissue sarcoma in patients who have received prior chemotherapy§ |

* Cabozantinib capsules (Cometriq) are approved for the treatment of metastatic medullary thyroid cancer. Cometriq will not be discussed in this review and is not interchangeable with cabozantinib (Cabometyx) tablets.

† Everolimus is also approved under the brand name Zortress® for prophylaxis of organ rejection in adult patients receiving a kidney transplant (at low-moderate immunologic risk) or liver transplant. Zortress will not be discussed in this review. Everolimus (Afinitor) is not indicated for the treatment of patients with functional carcinoid tumors.

‡ Afinitor tablets may be used for all approved indications; Afinitor Disperz is approved for the treatment of adult and pediatric patients SEGA associated with TSC and as adjuvant treatment with TSC associated with partial onset seizures.

§ The efficacy of pazopanib (Votrient) for the treatment of patients with adipocytic soft tissue sarcoma or GIST has not been demonstrated.

FDA-Approved Indications (continued)

| Drug | Manufacturer | Indication(s) |
|---|--------------|--|
| sorafenib (Nexavar®) ⁷ | Bayer | <ul style="list-style-type: none">Unresectable HCCAdvanced RCCLocally recurrent or metastatic progressive, differentiated thyroid carcinoma (DTC) refractory to radioactive iodine treatment |
| sunitinib malate (Sutent®) ⁸ | Pfizer | <ul style="list-style-type: none">Gastrointestinal stromal tumors (GIST) after disease progression on or intolerance to imatinib mesylateAdvanced RCCAdjuvant treatment of RCC at high risk of recurrence following nephrectomyProgressive well-differentiated pancreatic neuroendocrine tumors (PNET) in patients with unresectable, locally advanced, or metastatic disease |
| tivozanib (Fotivda®) ⁹ | Aveo | <ul style="list-style-type: none">Relapsed or refractory advanced RCC following ≥ 2 prior systemic therapies |

OVERVIEW

Renal cell carcinoma (RCC)

Cancers of the kidney and renal pelvis account for approximately 4% of all newly-diagnosed cancers in the United States (US), with a 5% incidence in males and a 3% incidence in females.^{10,11} The median age at diagnosis is 64 years, and > 75% of cases are diagnosed in patients ages 55 or older.¹² The overall 5-year survival for patients diagnosed with RCC was 75.6% from the period of 2011 to 2017.¹³ If the disease is localized at time of diagnosis, outcomes are excellent with a 5-year survival of approximately 93%; however, patients diagnosed with advanced, metastatic disease, accounting for approximately 16% of diagnoses, have much poorer outcomes with approximately a 14% survival rate at 5 years.¹⁴ Approximately 85% of kidney tumors are RCC, and approximately 70% of all RCC have a clear cell histology.¹⁵ Other less common histologies are usually grouped together as “non-clear cell” tumors. The incidence of RCC in men is more than twice that of women in the US.¹⁶ The most common presenting triad of symptoms includes hematuria, flank mass, and flank pain; however, as the use of routine imaging has become more widespread, the frequency of incidental detection of RCC has increased, and only about 30% of patients are now diagnosed on the basis of symptoms.¹⁷

Smoking, obesity, and hypertension are known environmental risk factors for the development of RCC.¹⁸ There are also hereditary types of RCC; von Hippel-Lindau (VHL) disease predisposes patients to the development of kidney cancer.¹⁹ In the US, kidney cancer death rates are highest among American Indians/Alaska natives.²⁰

Surgery is performed in most patients with RCC, using either a partial or radical nephrectomy depending on the stage and size of the tumor.²¹ After complete surgical resection of localized disease, 20% to 30% of patients will relapse. For select patients, those with stage 3 disease, clear cell histology and a high risk for relapse, adjuvant sunitinib may be utilized for 1 year (National Comprehensive Cancer Network [NCCN], category 2B). For patients with metastatic disease, careful patient selection is needed to determine who may benefit from cytoreductive surgery. Part of this selection process is based on the plan of therapy. Randomized trials have shown a benefit for cytoreductive surgery in patients who are then treated with historical immunotherapies, such as interferon, and retrospective data suggests that cytoreductive nephrectomy continues to play a role in patients treated with vascular endothelial growth factor (VEGF)-targeted agents.²² Initial trials in patients with advanced RCC who

were treated with targeted therapies (sunitinib [Sutent]) did not demonstrate a benefit in overall survival (OS) for patients who underwent nephrectomy followed by sunitinib, compared to sunitinib alone.²³ Further study is needed to define the role of cytoreductive nephrectomy with newly established therapeutic agents.

Traditional cytotoxic chemotherapy agents have demonstrated minimal efficacy against RCC. Typical response rates with these agents have been in the range of 4% to 6%.²⁴ Based on the historical observation that a very small percentage of patients with RCC will experience untreated, spontaneous disease regression, immunotherapy to evoke an enhanced immune system response was postulated. The first immunotherapy agents to demonstrate improved efficacy in the treatment of advanced RCC were the cytokines, interferon (IFN- α), and interleukin-2 (IL-2), with reported response rates ranging from 5% to 30%.²⁵ Despite the low response rate, a small subset of patients achieved durable partial or complete remissions with infusional IL-2 therapy, but the rates of severe toxicity are extremely high with this protocol. While high dose IL-2 is still listed as a first-line or subsequent therapy option in advanced RCC (category 2B), the recommendation for the use of interferon has been removed from the NCCN guidelines.²⁶ Targeted therapies utilizing tyrosine kinase inhibitors (TKIs) and immunotherapy checkpoint inhibitors, given either separately or in combination, have become the usual first- and second-line treatment options for advanced RCC due to their improved efficacy and tolerability compared to the cytokines. This review will focus on the role of the oral TKIs in the treatment of RCC.

The 1.2022 NCCN guidelines for first-line systemic therapy of favorable risk, clear cell histology, relapsed or stage 4 RCC recommend a TKI plus an immune checkpoint inhibitor (CPI) as the category 1, preferred options. Specifically, axitinib (Inlyta) plus pembrolizumab (Keytruda) or cabozantinib (Cabometyx) plus nivolumab (Opdivo) or lenvatinib (Lenvima) plus pembrolizumab are the 3 TKI/CPI regimens included. Other recommended regimens for this same group of patients include monotherapy with sunitinib (Sutent) or pazopanib (Votrient), or the combination of axitinib (Inlyta) plus avelumab (Bavencio, all NCCN category 2A). Axitinib monotherapy is a NCCN category 2B recommendation listed as useful in certain circumstances. For this same group of patients with poor or intermediate risk, rather than favorable risk, the same 3 TKI/CPI regimens are listed as category 1, preferred along with single agent cabozantinib being a category 2A, preferred option. Other options for these patients with poor or intermediate risk largely mirror the favorable risk options defined above. For subsequent therapy of RCC with clear cell histology, category 1, preferred options include cabozantinib and lenvatinib plus everolimus (Afinitor). Additional options include axitinib as either a single agent (category 1) or in combination with pembrolizumab (category 2A), cabozantinib plus nivolumab, lenvatinib plus pembrolizumab, or single agent pazopanib, sunitinib, or tivozanib (all category 2A). Everolimus as a single agent is included as a category 2A, useful in certain circumstances. For patients with non-clear cell histology, single agent cabozantinib, sunitinib, axitinib, pazopanib, and everolimus are all category 2A recommendations though cabozantinib and sunitinib are the preferred regimens. Importantly, sorafenib is now only included in the NCCN guidelines as a category 3 recommendation for subsequent therapy that may be useful in certain circumstances.

In 2017, sunitinib received FDA approval for use in the adjuvant setting of patients with RCC who have undergone nephrectomy but who are at a high risk of recurrence; however, NCCN guidelines have removed the recommendation for use of adjuvant sunitinib in patients with stage 2 disease, and the use of adjuvant sunitinib for 1 year in patients with stage 3 disease is an NCCN category 3 recommendation, indicating disagreement on the appropriateness of the intervention.²⁷

Miscellaneous Indications

Breast Cancer

For second- and subsequent-line therapy in postmenopausal or premenopausal women receiving ovarian ablation or suppression who have hormone-receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative recurrent or stage 4 breast cancer, the combinations of everolimus plus endocrine therapy is a NCCN category 2A, preferred recommendation.²⁸

Endometrial carcinoma

In 2021, there will be a projected 66,570 cases of endometrial (uterine corpus) cancer diagnosed and 12,940 deaths.²⁹ Endometrial cancer is rising in both incidence and associated mortality in the US.³⁰ Risk factors for the development of endometrial cancer include conditions leading to exposure of excess estrogen including obesity, hormone replacement with unopposed estrogen and estrogen-secreting tumors. Conversely, oral contraceptive use reduces the risk of endometrial cancer. In the US, 57% of all endometrial cancers are attributable to obesity. The average age at diagnosis is 63 years, but recent data show a sustained rise in cases among women under 50 years of age.³¹ According to the NCCN guidelines for Uterine Neoplasms **3.2021**, lenvatinib plus pembrolizumab is listed as a category 2A, useful in certain circumstances, second-line treatment option for recurrent, metastatic or high-risk endometrial carcinoma for patients without microsatellite instability (MSI)- high or deficient mismatch repair (dMMR) tumors.³²

Hepatocellular carcinoma (HCC)

The **3.2021** NCCN guidelines for hepatobiliary cancers list single agent sorafenib or **lenvatinib both as category 1, other recommended regimens** for patients with HCC and Child Pugh class A who have unresectable disease and are not transplant candidates.³³ Sorafenib in this setting is also an **other recommended regimen**, 2A recommendation for Child Pugh B7. Locoregional therapy (ablation, arterially-directed therapies, or radiation therapy) are usually preferred to systemic therapies in this setting.³⁴ TKIs with a category 1 recommendation for subsequent line therapy upon disease progression of HCC include single agent **regorafenib (Stivarga®) (category 1), cabozantinib (category 1)**, or lenvatinib (category 2A), all of which are restricted to patients with Child-Pugh Class A only. Sorafenib is a category 2A recommendation and is appropriate for patients with Child-Pugh Class A or B7.

Neuroendocrine Tumors (NET)

Everolimus and sunitinib are both category 1 recommendations in the NCCN **2.2021** neuroendocrine tumors guidelines for patients with NETs of the pancreas who have locoregional advanced disease and/or distant metastases who experience progressive disease.³⁵ Everolimus is also listed a category 2A recommendation for certain patients with locoregional, unresectable, advanced NETs originating from either the bronchopulmonary system or the thymus, depending on the tumor grade. For metastatic bronchopulmonary NET, everolimus is a category 1 recommendation. In addition, everolimus (category 2A, preferred) may be considered for patients with locoregional, advanced and/or metastatic neuroendocrine tumors originating in the gastrointestinal (GI) tract who experience disease progression after first-line therapy.

Soft Tissue Sarcoma

The 2.2021 NCCN soft tissue sarcoma (STS) guideline includes the use of pazopanib, sorafenib, and sunitinib when used as a single agents for the treatment of various soft tissue sarcomas, including angiosarcoma (all category 2A, other recommended regimens) and solitary fibrous tumor/hemangiopericytoma (all category 2A, preferred). Pazopanib and sunitinib are category 2A, preferred for alveolar soft part sarcoma.³⁶ For patients with soft tissue sarcomas with non-specific histologies, pazopanib is listed as being useful for first-line therapy in the metastatic setting when patients are ineligible for intravenous (IV) chemotherapy as well as in subsequent lines of therapy for advanced/metastatic disease (both category 2A). For desmoid tumors, sorafenib is a category 1, preferred recommendation for primary systemic therapy, while pazopanib is a category 2A, preferred option.³⁷

Sunitinib is a category 1, preferred recommendation for second-line therapy of unresectable recurrent or metastatic gastrointestinal stromal tumors (GIST) in patients who have experienced progressive disease on imatinib. Cabozantinib, pazopanib, sorafenib, and everolimus plus either imatinib, sunitinib, or regorafenib are all additional options after failure on approved therapies.³⁸

Thyroid Carcinoma

The main histologic types of thyroid carcinoma include differentiated thyroid carcinoma (including follicular, papillary and Hürthle cell histologies), medullary carcinoma, and anaplastic carcinoma. While anaplastic thyroid carcinoma is an aggressive undifferentiated tumor, the natural history of differentiated thyroid carcinoma (DTC) is variable; some patients may experience disease progression within months, while others may only have disease progression after several years. In addition, kinase inhibitor therapy is considered palliative in the setting of advanced thyroid carcinoma. These agents can be associated with improved progression-free survival (PFS) but are not considered curative. For these reasons, the pace of disease progression should be factored into treatment decisions with kinase inhibitors for DTC. Patients with very indolent DTC who are asymptomatic may not be good candidates for kinase inhibitor therapies, particularly if the side effects of treatment will adversely affect the patient's quality of life, while patients with more rapidly progressive DTC may derive benefits that outweigh drug-induced side effects. The 1.2021 NCCN guidelines regarding thyroid carcinoma state lenvatinib is the preferred agent for locally recurrent, advanced and/or metastatic, iodine-refractory, differentiated (follicular, papillary, Hürthle cell histologies) thyroid carcinoma, but sorafenib may also be considered. The guidelines state the decision of whether to use lenvatinib or sorafenib should be individualized for each patient based on the likelihood of response and comorbidities. Axitinib, cabozantinib, everolimus, pazopanib, and sunitinib are all category 2A options for these same patients if clinical trials are not available or appropriate.³⁹

For medullary thyroid carcinoma (MTC), cabozantinib is a category 1, preferred recommendation for patients with recurrent or persistent locoregional disease who are symptomatic. If the patient has persistent disease or distant metastases and is symptomatic, cabozantinib is a category 1, preferred option. Other options for symptomatic advanced disease include sorafenib, sunitinib, lenvatinib, or pazopanib, which are also listed as category 2A options.⁴⁰

Tuberous Sclerosis Complex

Tuberous sclerosis complex (TSC) is a genetic disease inherited in an autosomal dominant pattern that is associated with mutations in the TSC1 or TSC2 genes and can affect multiple organ systems. Patients

with TSC are susceptible to growth of non-malignant tumors in several organs including the skin, brain, kidneys, lungs, heart, liver, and eyes. Additionally, patients with TSC are at a very high risk of developing epilepsy and the majority of TSC patients begin to have seizures during the first year of life.⁴¹ Mutation in the TSC1/TSC2 genes has been shown to result in over activation of the mammalian target of rapamycin (mTOR) signaling pathway. While surgery is the mainstay of treatment for most tumors associated with TSC, mTOR inhibitors, including everolimus, have been shown to be effective in treating the manifestations of TSC. Subependymal Giant Cell Astrocytoma (SEGA) occurs in up to 20% of patients with TSC and most frequently occurs during childhood or adolescence. Everolimus is indicated in pediatric and adult patients with SEGA associated with TSC that requires therapeutic intervention but cannot be curatively resected. TSC-related renal angiomyolipomas carry a risk for bleeding and subsequent aneurysm based on the vascular nature of these tumors. In this setting, everolimus may be preferred over surgery in some adult patients due to the potential loss of renal function associated with surgery.⁴² Everolimus was also approved in 2018 for the adjunctive treatment of TSC-associated partial-onset seizures in patients aged 2 years and older.⁴³ The International TSC Consensus Group guidelines were last updated in 2013. These guidelines address the use of mTOR inhibitors for patients with growing but otherwise asymptomatic SEGA, giving a category 1 recommendation to SEGA lesions that are not amenable to gross total resection. According to these guidelines, an mTOR inhibitor is recommended as first-line therapy for asymptomatic, growing angiomyolipomas measuring > 3 centimeters (cm) in diameter. Further, mTOR inhibitors may be used to treat lymphangiomyomatosis (LAM) symptoms, including exertional dyspnea and shortness of breath.⁴⁴

PHARMACOLOGY^{45,46,47,48,49,50,51,52}

All of the agents included in this review, with the exception of everolimus (Afinitor), are classified as tyrosine kinase inhibitors (TKIs). Everolimus (Afinitor) is a mammalian target of rapamycin (mTOR) inhibitor. Broadly, these agents are classified as signal transduction inhibitors because they target intracellular signal transduction pathways. These signal transduction pathways are known to lead to uncontrolled cellular growth and proliferation, tumor metastasis, and prevention of apoptosis in malignant cells. Protein kinase inhibitors function by binding to the adenosine triphosphate (ATP) binding site found on receptor and non-receptor tyrosine kinase proteins. If the ATP binding site is occupied by a protein kinase inhibitor, ATP is unable to bind and, hence, cannot donate a phosphate group to the protein residue on the substrate and activate the target protein. Therefore, activation of downstream signaling pathways that could lead to uncontrolled tumor cell growth and differentiation are inhibited.

In the case of RCC, the tumor suppressor gene, von Hippel-Landau (VHL), has been found to be linked to clear cell RCC, the most common subtype of RCC. Inactivation of the VHL tumor suppressor gene is now recognized as the hallmark of clear cell RCC.⁵³ The VHL gene produces the VHL protein (pVHL). When VHL is mutated or inactivated, pVHL is unable to bind and target hypoxia-inducible factor (HIF)-1 α for degradation. This leads to overabundance of HIF-1 α which activates transcription of vascular endothelial growth factor (VEGF) and platelet derived growth factor (PDGF), as well as other kinases that are responsible for promoting angiogenesis and tumor development. The mechanism of action of several of the targeted therapies is to inhibit these kinases.

| | Tyrosine Kinase Inhibition | | | | | | | |
|--------------------------|----------------------------|------|------|-----|-------|------|------|-------|
| | Receptor | | | | | | | |
| | mTOR | cKIT | VEGF | RET | FLT-3 | PDGF | FGFR | c-MET |
| axitinib (Inlyta) | | | X | | | X | | |
| cabozantinib (Cabometyx) | | X | X | X | X | | X | X |
| everolimus (Afinitor) | X | | X | | | | | |
| lenvatinib (Lenvima) | | X | X | X | | X | X | |
| pazopanib (Votrient) | | X | X | | | X | X | |
| sorafenib (Nexavar) | | X | X | X | X | X | | |
| sunitinib (Sutent) | | X | X | X | X | X | X | |
| tivozanib (Fotivda) | | X | X | | | X | | |

PHARMACOKINETICS^{54,55,56,57,58,59,60,61}

| Drug | Half-Life (hr) | Protein binding (%) | Metabolism | Active Metabolites | Elimination (%) | Effect of a High Fat Meal (%) |
|--------------------------|----------------|---------------------|--|----------------------------------|-------------------------------|-------------------------------|
| axitinib (Inlyta) | 2.5-6.1 | > 99 | CYP3A4/5: major CYP1A2, CYP2C19, and UGT1A1: minor | N-glucuronide, sulfoxide | Feces: 41 Urine: 23 | AUC: ▲ 19 |
| cabozantinib (Cabometyx) | 99 | > 99 | CYP3A | none | Feces: 54 Urine: 27 | AUC: ▲ 57 Cmax: ▲ 41 |
| everolimus (Afinitor)* | 30 | 74 | CYP3A4; P-gP | none | Feces: 80 Urine: 5 | Cmax: ▼ 42-60 AUC: ▼ 16-32 |
| lenvatinib (Lenvima) | 28 | 98-99 | CYP3A | none | Feces: 64 Urine: 25 | Tmax ▲ 100 |
| pazopanib (Votrient) | 30.9 | > 99 | CYP3A4: major CYP1A2, 2C8: minor | none | Feces: majority Urine: < 4 | AUC: ▲ 100 Cmax: ▲ 100 |
| sorafenib (Nexavar) | 25-48 | 99.5 | CYP3A4; glucuronidation by UGT1A9 | Pyridine N-oxide | Feces: 77 Urine: 19 | Bioavailability: ▼ 29 |
| sunitinib (Sutent) | 40-60 | 95 | CYP3A4 | yes (half-life 80- 110 hours) | Feces: 61 Urine: 16 | none |
| tivozanib (Fotivda) | 111 | ≥ 99% | CYP 3A4 | none | Feces: 79 Urine: 12 | none |

hr = hours

* Afinitor Disperz has an equivalent area under the curve (AUC) to Afinitor but the maximum plasma concentration (C_{max}) is 20% to 36% lower.

CONTRAINDICATIONS/WARNINGS^{62,63,64,65,66,67,68,69}

Contraindications

There are no contraindications with axitinib (Inlyta), cabozantinib (Cabometyx), lenvatinib (Lenvima), pazopanib (Votrient), sunitinib (Sutent), or tivozanib (Fotivda).

Everolimus (Afinitor, Afinitor Disperz) and sorafenib (Nexavar) are contraindicated in patients with hypersensitivity to the active drug or any of the components. Everolimus (Afinitor, Afinitor Disperz) is also contraindicated in patients with hypersensitivity to any other rapamycin derivatives.

Sorafenib (Nexavar) in combination with carboplatin and paclitaxel is contraindicated in patients with squamous cell lung cancer. A randomized controlled trial in chemotherapy-naïve patients with stage IIIB-IV non-small cell lung cancer which compared the safety and efficacy of carboplatin and paclitaxel, with or without sorafenib (Nexavar), was terminated early because overall survival was not improved with the addition of sorafenib (Nexavar).⁷⁰ In the subset analysis of patients with squamous cell carcinoma, higher mortality was observed with the addition of sorafenib (Nexavar) compared to those treated with carboplatin and paclitaxel alone (hazard ratio [HR], 1.81, 95% confidence interval [CI], 1.19 to 2.74). No definitive cause was identified for this finding.

Boxed Warnings

Pazopanib (Votrient) carries a boxed warning related to hepatotoxicity manifested as increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin. Hepatotoxicity can be severe and fatal. Transaminase (ALT, AST) elevations occur early in the course of treatment (92.5% of any grade occurred in the first 18 weeks). Liver function tests (LFTs) should be performed prior to initiation of therapy and at weeks 3, 5, 7, and 9. Thereafter, monitor at month 3 and at month 4, and as clinically indicated. After month 4, periodic monitoring should continue. Patients with isolated ALT elevations between 3 to 8 times the upper limit of normal (ULN) may continue on pazopanib (Votrient) with weekly monitoring of liver function until ALT returns to grade 1 or baseline. Patients with isolated ALT elevations of greater than 8 times the ULN should temporarily discontinue pazopanib (Votrient) therapy until levels return to grade 1 or baseline. If the potential benefit of pazopanib (Votrient) therapy outweighs the risk of hepatotoxicity, then reintroduce pazopanib (Votrient) at a reduced dose of no more than 400 mg daily, and measure serum liver function tests weekly for 8 weeks. If ALT elevations of greater than 3 times ULN recur, then pazopanib (Votrient) therapy should be permanently discontinued. If ALT elevations greater than 3 times ULN occur concurrently with bilirubin elevations greater than 2 times ULN, pazopanib (Votrient) should be permanently discontinued. Patients should be monitored until resolution.

Pazopanib (Votrient) is a UGT1A1 inhibitor. Mild, indirect (unconjugated) hyperbilirubinemia may occur in patients with Gilbert's syndrome. Patients with only a mild indirect hyperbilirubinemia and elevation in ALT greater than 3 times the ULN should be managed as per the recommendations outlined for isolated ALT elevations. The safety of pazopanib (Votrient) in patients with pre-existing severe hepatic impairment, defined as total bilirubin greater than 3 times the ULN with any level of ALT, is unknown. Treatment with pazopanib (Votrient) is not recommended in patients with severe hepatic impairment.

Sunitinib (Sutent) labeling has a boxed warning regarding hepatotoxicity that has been observed in clinical trials and post-marketing experience. Hepatotoxicity can be severe and fatal. LFTs should be monitored (ALT, AST, bilirubin) before initiation of treatment, during each treatment, and as clinically indicated. Treatment with sunitinib (Sutent) should be interrupted for grade 3 or 4 drug-related hepatic adverse events and discontinued if there is no resolution. Sunitinib (Sutent) should not be restarted if patients subsequently experience severe changes in LFTs or exhibit other signs and symptoms of liver failure. Safety of sunitinib (Sutent) in patients with ALT or AST greater than 2.5 times the ULN or, if due to liver metastases, greater than 5 times the ULN has not been established.

Selected Warnings and Recommended Monitoring

| Drug | Selected Warnings | Recommended Monitoring |
|--------------------------|---|--|
| axitinib (Inlyta) | Hypertension (hypertensive crisis); arterial/venous thrombotic events; hemorrhage (sometimes fatal); GI perforation; fistula; thyroid dysfunction; reversible posterior leukoencephalopathy syndrome (RPLS); proteinuria; increased LFTs/bilirubin, which can occur with higher frequency when given in combination with avelumab or pembrolizumab; cardiac failure; when given in combination with avelumab, major adverse cardiovascular events (MACE) including myocardial infarction, congestive heart failure, and death due to cardiac events; hold axitinib at least 2 days prior to scheduled surgery and for at least 2 weeks following major surgery, then resume therapy based on clinical judgement of adequate wound healing | Blood pressure, thyroid function, urinary protein, ALT, AST, bilirubin (more frequently in patients receiving combination therapy with avelumab or pembrolizumab), baseline and periodic evaluations of left ventricular ejection fraction, signs/symptoms of cardiac failure, neurologic symptoms, sign/symptoms of bleeding, symptoms of GI perforation or fistula |
| cabozantinib (Cabometyx) | Hemorrhage, GI perforations and fistulas, thrombotic events, hypertension and hypertensive crisis, diarrhea, palmar-plantar erythrodysesthesia syndrome (PPES), RPLS, embryo-fetal toxicity, proteinuria, osteonecrosis of the jaw, wound complications, hold cabozantinib for at least 3 weeks prior to elective surgery and for at least 2 weeks following major surgery; when given in combination with nivolumab, hepatic toxicity can occur with higher frequencies of \geq grade 3; primary or secondary adrenal insufficiency | Blood pressure prior to initiation and regularly during treatment; symptoms of fistulas and perforations; when given in combination with nivolumab, monitor liver enzymes initially, periodically, and more frequently than when given alone; jaundice, severe nausea or vomiting; easy bruising or bleeding |

Selected Warnings and Recommended Monitoring (continued)

| Drug | Selected Warnings | Recommended Monitoring |
|--|--|--|
| everolimus (Afinitor, Afinitor Disperz) | Non-infectious pneumonitis (fatal cases reported) some cases with pulmonary hypertension (including pulmonary arterial hypertension), infections (some fatal), severe hypersensitivity reactions, myelosuppression, stomatitis, embryo-fetal toxicity, angioedema with concomitant angiotensin converting enzyme (ACE) inhibitors, oral ulcerations, impaired wound healing, metabolic disorders (hyperglycemia, hyperlipidemia, hypertriglyceridemia), decreased hemoglobin, lymphocytes, neutrophils and platelets, renal failure (including acute renal failure) some fatal, risk of embryo-fetal toxicity, impaired wound healing, hold everolimus for at least 1 week prior to elective surgery and for at least 2 weeks following major surgery; radiation sensitization (esophagitis and pneumonitis), including severe reactions | Pulmonary signs/symptoms, signs/symptoms of infections, serum creatinine, blood urea nitrogen (BUN), urinary protein, completed blood count (CBC), serum glucose, lipids; cutaneous and visceral organ sensitization with radiation treatment |
| lenvatinib (Lenvima) | Hypertension, including serious complications of poorly controlled hypertension, cardiac dysfunction (decreased left or right ventricular function, cardiac failure, pulmonary edema), arterial thromboembolic events, hepatotoxicity (including fatal events) and acute hepatitis, proteinuria, diarrhea, renal impairment or failure, GI perforation and fistula formation, QT interval prolongation, hypocalcemia, RPLS, hemorrhagic events, thyroid dysfunction, embryo-fetal toxicity, wound healing complications (including fistula), hold lenvatinib for at least 1 week prior to elective surgery and for at least 2 weeks following major surgery; osteonecrosis of the jaw | Blood pressure after 1 week, then every 2 weeks for the first 2 months and then at least monthly thereafter; signs/symptoms of cardiac decompensation; LFTs/bilirubin prior to initiation, then every 2 weeks for the first 2 months and at least monthly thereafter; urine dipstick for proteinuria before initiation and periodically throughout treatment; dehydration; serum electrolytes; electrocardiograms in patients with congenital long QT syndrome; congestive heart failure (CHF); bradyarrhythmias or those taking drugs known to prolong QT interval; serum calcium levels at least monthly; thyroid function before initiation of and at least monthly |
| pazopanib (Votrient) | Increases in serum transaminases and bilirubin; hepatotoxicity (sometimes fatal); QT prolongation and torsades de pointes, decreased left ventricular ejection fraction (LVEF), CHF, hemorrhagic events, GI perforation and fistula formation, hemorrhage, hypertension (hypertensive crisis reported), arterial thromboembolic events including myocardial infarction and cerebrovascular accident (CVA), venous thromboembolic events including fatal pulmonary emboli (PE), thrombotic microangiopathy, hypothyroidism, proteinuria, infections with or without neutropenia (sometimes fatal), RPLS, interstitial lung disease (ILD)/pneumonitis, embryofetal toxicity, tumor lysis syndrome, impaired wound healing | LFTs and bilirubin prior to treatment and at weeks 3, 5, 7 and 9 as well as month 3 and month 4 and as clinically indicated; electrocardiogram (ECG); chemistry panel plus calcium, phosphate and magnesium; signs/symptoms of bleeding; measure blood pressure within 1 week after starting therapy and frequently thereafter; baseline and periodic evaluation of LVEF in patients at risk for cardiac dysfunction; signs and symptoms of thrombotic microangiopathy; thyroid function tests; urinary protein; serum lipase/amylase; signs/symptoms of infection; CHF; venous thromboembolism (VTE) or PE; pulmonary symptoms indicative of ILD/pneumonitis; close monitoring of patients at risk of tumor lysis syndrome (TLS), including those with rapidly growing tumors, high tumor burden, renal dysfunction or dehydration, consider TLS prophylaxis for appropriate patients |

Selected Warnings and Recommended Monitoring (continued)

| Drug | Selected Warnings | Recommended Monitoring |
|------------------------|--|--|
| sorafenib (Nexavar) | Cardiac ischemia/infarction, congestive heart failure, QT prolongation/ventricular arrhythmia, hemorrhage, hypertension, dermatological toxicities including hand-foot skin reaction and rash, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), GI perforation, elevation of INR when given with warfarin, wound healing complications, drug interactions with UGT1A1 substrates (irinotecan), docetaxel, and doxorubicin; caution in patients with hepatic impairment, drug-induced hepatitis (sometimes hepatic failure/death), impairment of TSH suppression in DTC, embryofetal toxicity | Signs/symptoms of cardiac ischemia; ECG/electrolytes in patients with CHF; bradyarrhythmias or drugs known to prolong the QT interval; signs/symptoms of bleeding; CBC; serum phosphate; weekly blood pressure for first 6 weeks, followed by normal medical protocol thereafter; LFTs; TSH levels in patients with DTC |
| sunitinib (Sutent) | Heart failure, myocardial disorders and cardiomyopathy; left ventricular dysfunction (discontinue if clinical evidence of CHF); hemorrhagic events; QT prolongation and torsades de pointes, hypertension; thyroid dysfunction; adrenal insufficiency; hepatotoxicity (including liver failure or death); impaired wound healing (osteonecrosis of the jaw; tumor lysis syndrome; proteinuria and nephrotic syndrome; severe cutaneous reactions including erythema multiforme, SJS and TEN, some fatal; discontinue sunitinib if erythema multiforme, SJS or TEN occurs; necrotizing fasciitis, including fatal cases have occurred; thrombotic microangiopathy; hypothyroidism, hyperthyroidism, and thyroiditis; hypoglycemia; RPLS; embryofetal toxicity | CBC with platelet count, ECG (QT interval with ECGs should be monitored more frequently when sunitinib is coadministered with medications known to prolong QT interval), chemistry panel, phosphate magnesium, LVEF, LFTs, signs/symptoms of CHF, baseline and periodic evaluation of LVEF, blood pressure, thyroid function tests, adrenal function, oral examination prior to initiation, monitor urine protein, interrupt treatment for 24-hour urine protein > 3 grams, discontinue for repeat episodes of urine protein > 3 grams despite dose reductions or nephrotic syndrome, adrenocorticotrophic hormone (ACTH) stimulation testing for adrenal insufficiency, neurologic symptoms |
| tivozanib (Fotivda) | Hypertension and hypertensive crisis; serious, sometimes fatal, cardiac failure; serious cardiac ischemia and arterial thromboembolic events leading to fatal outcomes; serious venous thromboembolic events including death; proteinuria, including grade 3 events; thyroid dysfunction; impair wound healing; RPLS; embryofetal toxicity; allergic reactions | Blood pressure should be controlled before initiation and monitored after 2 weeks and then at least monthly; any new onset of chest discomfort, sudden weakness, or other events suggestive of a thrombotic event, dyspnea or localized limb edema; any unusual bleeding or hemorrhage; proteinuria prior to initiation and periodically; thyroid function before initiation and periodically; wound healing; seizures, headaches, visual disturbances, confusion, or difficulty thinking |

DRUG INTERACTIONS^{71,72,73,74,75,76,77,78}

CYP3A4 substrates – Enzyme Inhibition and Induction

Co-administration of CYP3A4 Inhibitors

All of the agents included in this review are substrates for the cytochrome P450 3A4 (CYP3A4) enzyme. When co-administered with potent inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, ritonavir, saquinavir, telithromycin), plasma concentrations of all the agents in this category can potentially increase. In addition, patients taking any of the medications included in this review should avoid grapefruit juice as it can increase the plasma concentrations of these agents.

Concomitant administration with potent inhibitors of CYP3A4 and the agents included in this review should be avoided, and selection of an alternate medication with minimal to no enzyme inhibition potential is recommended. However, if 1 of these agents must be co-administered with a CYP3A4 inhibitor, caution should be exercised and/or a dose reduction considered. No dose adjustment is recommended with lenvatinib (Lenvima) due to any known drug interactions. Specific dose modifications for pazopanib (Votrient) recommend reducing the dose to 400 mg if administered with a strong CYP3A4 inhibitor and further dose reductions may be needed if adverse effects occur during therapy. Everolimus (Afinitor) dose should be reduced to 2.5 mg daily if co-administered with a moderate CYP3A4 inhibitor, such as erythromycin or fluconazole. If the moderate inhibitor is discontinued, a washout period of approximately 2 to 3 days should be allowed before the everolimus (Afinitor) dose is increased to the original dose. Cabozantinib (Cabometyx) dose should be reduced if given with concomitant strong CYP3A4 inhibitors. Specific dose modifications and serum trough level concentration targets are provided in the package insert when this drug interaction occurs in patients receiving everolimus (Afinitor) for the treatment of SEGA with TSC.

Co-administration of CYP3A4 Inducers

Administration of all of these with potent inducers of CYP3A4 (e.g., dexamethasone, phenytoin, phenobarbital, carbamazepine, rifampin, rifabutin) may result in decreases in plasma concentrations of these agents. Axitinib (Inlyta) and pazopanib (Votrient) should not be used if concomitant use of strong CYP3A4 inducers cannot be avoided. If co-administration of everolimus (Afinitor) and a strong CYP3A4 inducer must be administered, consider doubling the dose of everolimus (Afinitor) in increments of 5 mg or less. If the strong inducer is discontinued, consider a washout period of 3 to 5 days before everolimus (Afinitor) dose is returned to the original dose. No dose adjustment is recommended for lenvatinib (Lenvima) when co-administered with CYP3A4 inducers. Specific dose modifications and serum trough level concentration targets are provided in the package insert when this drug interaction occurs in patients receiving everolimus (Afinitor) for the treatment of SEGA with TSC. Increase the dose of cabozantinib (Cabometyx) with concomitant use of a strong CYP3A4 inducer. Concurrent use of the rest of these agents with strong inducers of CYP3A4 should be avoided or used with caution. If these other agents must be used with a CYP3A4 inducer, a dose increase should be considered. Moderate CYP3A4 inducers (e.g., efavirenz, modafinil) may also reduce the plasma exposure of axitinib (Inlyta) and should be avoided if possible.

St. John's wort

St. John's wort is an inducer of CYP3A4 and may unpredictably reduce plasma concentrations of everolimus (Afinitor), sunitinib (Sutent), and tivozanib (Fotivda). Use of this herbal product should be avoided with these agents.

Substrates of CYP3A4

Pazopanib (Votrient) and sorafenib (Nexavar) are also inhibitors of CYP3A4 and, when co-administered with drugs eliminated by this enzyme, they have the potential to increase the plasma concentrations of the CYP3A4 substrates. Caution is advised when using these agents with CYP3A4 substrates that have a narrow therapeutic index (e.g., alfentanil, cyclosporine, ergot alkaloids, fentanyl, pimozone, quinidine, sirolimus, and tacrolimus).

CYP2B6 and CYP2C8 Enzyme Substrates

Pazopanib (Votrient) is also a weak inhibitor of CYP2D6 and CYP2C8. Concomitant use of narrow therapeutic drugs metabolized by these pathways should be avoided.

P-glycoprotein (P-gP) Inhibitors and Substrates

Everolimus (Afinitor) is partially metabolized by the multidrug efflux pump P-gP and should not be used with strong inhibitors of P-gP (e.g., erythromycin, verapamil, and cyclosporine). Use caution when administering everolimus (Afinitor) in combination with moderate P-gP inhibitors and, if alternative treatment cannot be administered, reduce the everolimus (Afinitor) dose. Pazopanib (Votrient) is also a substrate of P-gP, as well as breast cancer resistance protein. Concomitant treatment with strong inhibitors of P-gP should be avoided with pazopanib (Votrient) due to the risk of increased exposure to pazopanib (Votrient).

Live Vaccines

The use of live vaccines and close contact with those who have received live vaccines should be avoided during treatment with everolimus (Afinitor). Examples of live vaccines are intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines. The timing of routine vaccinations in pediatric patients with SEGA should be considered before initiating everolimus (Afinitor) therapy.

Warfarin

Elevations in INR have been reported in some patients taking sorafenib (Nexavar) in addition to warfarin.

Other Medications

Co-administration of everolimus (Afinitor) and depot octreotide increased octreotide minimum serum concentrations levels by 50%.

Pazopanib (Votrient) is not indicated for use in combination with other agents. Clinical trials of pazopanib (Votrient) in combination with pemetrexed and lapatinib were terminated early due to concerns over increased toxicity and mortality. Thrombotic microangiopathy has been reported with pazopanib (Votrient) used in combination with bevacizumab or topotecan, as well as during monotherapy.

Concomitant use of pazopanib (Votrient) and simvastatin increases the incidence of ALT elevations. If a patient receiving this combination develops ALT elevations, the dose may need to be adjusted or consideration given to discontinuing simvastatin.

Concomitant use of pazopanib (Votrient) with drugs that raise gastric pH, such as antacids, proton pump inhibitors (PPIs), or histamine-receptor antagonists (H2RA), should be avoided. If such drugs are needed, short-acting antacids should be considered in place of PPIs and H2RAs.

Co-administration of oral neomycin decreases sorafenib (Nexavar) exposure.

ADVERSE EFFECTS^{79,80,81,82,83,84,85,86}

| Drug | Fluid Retention/ Edema | Diarrhea | Headache | Skin Rash | Nausea | Hemorrhage | Muscle Pain/ Myalgia | Stomatitis | Anemia | HTN |
|--|---------------------------|------------|------------|------------|------------|------------------------|-------------------------|------------|------------|------------|
| axitinib (Inlyta) n=359 | nr | 55 | 14 | 13 | 32 | epistaxis 6 | 7 | 15 | 4-35 | 40 |
| axitinib (Inlyta) + avelumab (Bavencio) (n=434) versus sunitinib (Sutent) (n=439) RCC | nr | 62 (48) | 21 (16) | 25 (16) | 34 (39) | nr | 40 (33) | 34 (35) | 21 (65) | 50 (36) |
| axitinib (Inlyta) + pembrolizumab (Keytruda) (n=429) versus sunitinib (n=425) RCC | nr | 56 (45) | nr | 25 (21) | 28 (32) | nr | nr | 27 (41) | 29 (65) | 48 (48) |
| cabozantinib (Cabometyx) n=331 RCC (everolimus, n=322) | nr | 74 (28) | 11 (12) | 23 (43) | 50 (28) | nr | nr | 22 (24) | 31 (71) | 39 (28) |
| everolimus (Afinitor) n=274 RCC | 25 (8) | 30 (7) | 19 (9) | 29 (7) | 26 (19) | epistaxis 18 (0) | 10 (7) | 44 (0) | 92 (79) | nr |
| everolimus (Afinitor) n=204 PNET | 39 (12) | 50 (25) | 30 (15) | 59 (19) | 32 (33) | nr | 15 (7) | 70 (20) | 86 (63) | 13 (6) |
| everolimus (Afinitor) n=274 renal angiomyolipoma with TSC | 13 (8) | 14 (5) | 22 (21) | 5 | 16 (13) | epistaxis 9 | 13 (5) | 78 (23) | 61 (49) | reported |
| everolimus (Afinitor) n=274 SEGA | 4 | 25 | 18 | 18 | nr | nr | nr | 86 | 39 | 4 |
| everolimus (Afinitor) n=274 Advanced HR+BC | 19 (6) | 33 (18) | 21 (14) | 39 (6) | 29 (28) | nr | 20 (17) | 67 (11) | 68 (40) | nr |
| lenvatinib (Lenvima) + everolimus (n=62) RCC (everolimus) n=50 | 42 (20) | 81 (34) | 19 (10) | 35 (40) | 45 (16) | 32 (26) | 55 (32) | 44 (50) | 8 (nr) | 42 (10) |
| lenvatinib (Lenvima) n=392 DTC | 21 (8) | 67 (17) | 38 (11) | 21 (3) | 47 (25) | nr | 62 (28) | 41 (8) | nr | 73 (16) |

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for placebo group are reported in parentheses. nr = not reported.

Adverse Effects (continued)

| Drug | Fluid Retention/ Edema | Diarrhea | Headache | Skin Rash | Nausea | Hemorrhage | Muscle Pain/ Myalgia | Stomatitis | Anemia | HTN |
|---|---------------------------|------------|------------|------------|------------|------------|-------------------------|------------|------------|------------|
| lenvatinib (Lenvima) + pembrolizumab (n=94) EC | nr | 64 | 33 | 21 | 48 | 28 | 65 | 43 | nr | 65 |
| pazopanib (Votrient) n=290 RCC | nr | 52 (9) | 10 (5) | 8 (3) | 26 (9) | 13 (5) | nr | nr | nr | 40 (10) |
| sorafenib (Nexavar) n=297 HCC | nr | 55 (25) | nr | 19 (14) | 24 (20) | 18 (20) | > 10 | 1- < 10 | nr | 9 (4) |
| sorafenib (Nexavar) n=451 RCC | nr | 43 (13) | 10 (6) | 40 (16) | 23 (19) | 15 (8) | > 10 | 1- < 10 | 44 (49) | 17 (2) |
| sorafenib (Nexavar) n=207 DTC | nr | 68 (15) | 17 (6) | 35 (7) | 21 (12) | nr | 10 (3) | 24 (3) | nr | 41 (12) |
| sunitinib (Sutent) n=202 GIST | nr | 40 (27) | nr | 14 (9) | ≥ 20 | 18 (17) | 14 (9) | 29 (18) | 26 (22) | 15 (11) |
| sunitinib (Sutent) n=375 metastatic RCC | 11 | 58 | 18 | 27 | 49 | 37 | 17-19 | 43 | 71 | 30 |
| sunitinib (Sutent) n=86 PNET | nr | 59 (39) | 18 (13) | 18 (5) | 45 (29) | 22 (10) | 15 (6) | 48 (18) | 65 (55) | 27 (5) |
| sunitinib (Sutent) n=610 adjuvant RCC | 18 (< 1) | 57 (22) | 19 (12) | 24 (12) | 34 (15) | 24 (5) | 11 (10) | 61 (15) | nr | 39 (14) |
| tivozanib (Fotivda) (n=173) versus sorafenib (Nexavar) (n=170) metastatic RCC | nr | 43 (54) | nr | 18 (52) | 30 (18) | 17 (12) | 19 (16) | 21 (23) | nr | 44 (31) |

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for placebo group are reported in parentheses. nr = not reported.

Other common (≥ 20%) adverse reactions seen in clinical trials with axitinib included fatigue, decreased appetite, dysphonia, palmar-plantar erythrodysesthesia (hand-foot) syndrome (PPES), weight decrease, vomiting, asthenia, and constipation.

Other adverse reactions occurring in ≥ 25% of RCC patients treated in clinical trials of cabozantinib included fatigue, decreased appetite, PPES, vomiting, weight decrease, and constipation. **Vascular disorders (arterial [including aortic] aneurysms, dissections, and rupture) have been reported in postmarketing experience with axitinib, cabozantinib, lenvatinib, pazopanib, sorafenib, and sunitinib.**

For RCC patients treated with everolimus in clinical trials, ≥ 30% also experienced infections, asthenia, fatigue, and cough. Adverse reactions reported in post marketing experience with everolimus for all approved indications have included acute pancreatitis, cholecystitis,

cholelithiasis, arterial thrombotic events, reflex sympathetic dystrophy, and cardiac failure with some cases reported with pulmonary hypertension (including pulmonary arterial hypertension) as a secondary event.

Post marketing events reported with lenvatinib for any FDA-approved indication have included increase amylase, pancreatitis, and cholecystitis.

In the RCC studies of pazopanib, $\geq 20\%$ of patients also experienced fatigue, anorexia, vomiting, and hair color change. Post marketing reports related to the use of pazopanib for any FDA-approved indication have included retinal detachment/tear and pancreatitis. In a pooled analysis of clinical trials, grade 3 and grade 4 adverse reactions were observed more frequently in patients of East Asian descent than in patients of non-East Asian descent for neutropenia (12% versus 2%), thrombocytopenia (6% versus $< 1\%$), and PPES (6% versus 2%).

Other common ($\geq 20\%$) adverse reactions to sorafenib seen in patients with HCC, RCC, or DTC include fatigue, infection, alopecia, hand-foot skin reaction, weight loss, decreased appetite, and abdominal pain. Post-marketing adverse reaction reports regarding sorafenib have included Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), angioedema, rhabdomyolysis, osteonecrosis of the jaw, and interstitial lung disease-like events (which may have a life-threatening or fatal outcome).

Post marketing reports regarding sunitinib use for any indication have included esophagitis, cholecystitis, serious infection (with or without neutropenia), fistula formation, myopathy and/or rhabdomyolysis, with or without acute renal failure, deep vein thrombosis, pulmonary embolism, pyoderma gangrenosum, cerebrovascular accident, transient ischemic attack, and cerebral infarction.

Other common ($\geq 15\%$) adverse reactions seen in clinical trials with tivozanib included fatigue, vomiting, decreased appetite, dysphonia, cough, dyspnea, hypothyroidism, PPES, and weight decrease.

Toxicities

There are numerous published meta-analyses examining adverse effects associated with vascular endothelial growth factor (VEGF) and tyrosine kinase inhibitors (TKIs) both as a class and as individual drugs. The findings of those meta-analyses are summarized in the table below.

| Toxicity | Drug(s) | Pertinent Findings |
|---|-----------------------------------|---|
| anemia, thrombocytopenia ^{87,88} | everolimus (n=3,679) | relative risk (RR) all-grade anemia = 2.18 (p<0.001); RR of high-grade anemia = 2.63 (p<0.001); highest risk for anemia was seen in RCC patients |
| | everolimus/temsirolimus (n=5,436) | significantly increased risk of all-grade anemia, high-grade anemia, all-grade thrombocytopenia, and high-grade thrombocytopenia |
| arterial thromboembolic events ⁸⁹ | sunitinib, sorafenib (n=10,255) | RR = 3.03 (p=0.15; not significant) |
| cardiovascular (hypertension, LV dysfunction, bleeding or thrombosis) ⁹⁰ | VEGF-TKIs (n=11,612) | RR all-grade HTN = 2.78 (p<0.00001); bleeding RR = 1.93 (p<0.00001); thrombosis RR = 0.85 (p=0.5; not significant); cardiac dysfunction RR = 2.36 (p=0.06; not significant) |

Toxicities (continued)

| Toxicity | Drug(s) | Pertinent Findings |
|--|---|---|
| congestive heart failure ^{91,92} | VEGF-TKIs (n=10,647) | VEGF-TKIs: RR = 2.69 (p<0.001) |
| | sunitinib (n=6,935) | sunitinib: RR all grade CHF = 1.81 (p<0.001) |
| fatigue ^{93,94} | VEGF-TKIs/mTOR inhibitors (n=7,304) | RR all-grade fatigue = 1.35 (p<0.001); RR of high-grade fatigue = 1.33 (p=0.08; not significant) |
| | everolimus, temsirolimus (n=9,760) | RR all-grade fatigue = 1.22 (p=0.002); high-grade fatigue RR = 1.82 (Pp=0.002) |
| gastrointestinal ⁹⁵ | VEGF-TKIs (n=6,447) | diarrhea was the most common GI event, which was significantly higher in RCC compared to other cancers; in RCC patients, sorafenib was associated with lower incidence of all-grade GI events compared to sunitinib (p<0.001) and a lower incidence of all-grade GI effects and high-grade anorexia compared to pazopanib (p<0.001) |
| gastrointestinal perforation ⁹⁶ | VEGF-TKIs (n=5,352) | no significant increased risk of GI perforation compared to control |
| hand-foot skin reaction (HFSR) / palmar-plantar erythrodysesthesia (hand-foot) syndrome (PPES) ⁹⁷ | axitinib (n=984) | RR all-grade HFSR=0.54 (p<0.001); RR of high-grade HFSR=0.31 (p<0.001); sorafenib, sunitinib, and axitinib had a significantly higher incidence as compared to pazopanib |
| hepatic toxicity (ALT, AST, total bilirubin increases) ^{98,99} | VEGF-TKIs (n=3,691) | RR of ALT increase: significant for sorafenib and pazopanib, but not sunitinib; higher RR of any grade AST increase for all drugs evaluated; a higher RR for any grade bilirubin elevation associated with pazopanib or regorafenib but not for sunitinib |
| | pazopanib (n=1,478) | RR high-grade AST elevation = 6.56 (p=0.002); RR high-grade ALT elevation = 4.33 (p=0.001); the risks of high-grade bilirubin elevation and fatal hepatotoxicity were not statistically significantly different than placebo |
| hypertension ¹⁰⁰ | axitinib (n=1,908) | RR all-grade hypertension = 3 (p=0.11); RR high-grade hypertension = 1.71 (p=0.003); risk of hypertension was significantly higher in RCC compared with non-RCC patients |
| infections ¹⁰¹ | everolimus/temsirolimus (n=3,180) | RR all-grade infections = 2 (p<0.001); RR high-grade infections = 2.6 (p<0.001) |
| metabolic complications (hyperglycemia, hypercholesterolemia, hypertriglyceridemia) ¹⁰² | mTOR inhibitors (everolimus, temsirolimus, ridaforolimus [not available in US]) (n=4,261) | statistically significant increase in the risk of hyperglycemia, hypercholesterolemia, and hypertriglyceridemia with mTOR inhibitors compared to control |

Toxicities (continued)

| Toxicity | Drug(s) | Pertinent Findings |
|---|--|--|
| pancreatitis ¹⁰³ | VEGF-TKIs (n=10,578) | RR all-grade pancreatitis = 1.95 (p=0.042); RR high-grade pancreatitis 1.89 (p=0.069; not significant) |
| pruritus ¹⁰⁴ | targeted therapies (VEGF-TKIs, monoclonal antibodies) (n=20,532) | RR all-grade pruritus = 2.9 (p<0.001) |
| QTc prolongation/serious arrhythmias ¹⁰⁵ | VEGF-TKIs (n=6,548) | RR all-grade QTc prolongation = 8.66 (p<0.11); RR of high grade QTc prolongation = 2.69 (p=0.006); subgroup analysis revealed only sunitinib and vandetanib had a statistically significant risk of QTc prolongation |
| rash ¹⁰⁶ | everolimus (n=2,242) | RR all-grade rash = 3.853 (p=0.001); RR high-grade rash = 2.997 (not significant) |
| stomatitis ^{107,108} | everolimus/temsirolimus (n=4,752) | RR all-grade stomatitis = 4.04 (p<0.001); RR of high-grade stomatitis = 8.84 (p<0.001) |
| | everolimus (10 clinical trials) | significantly increased risk of all-grade stomatitis, skin rash, pruritus and mouth ulceration |
| thyroid dysfunction ¹⁰⁹ | VEGF-TKIs (12 clinical trials) | RR = 3.59 (p<0.0001) |
| treatment related mortality ^{110,111} | everolimus (n=2,997) | a small but significant increase in the odds of treatment-related fatal events |
| | everolimus/temsirolimus (n=3,193) | |
| venous thromboembolism ^{112,113} | VEGF-TKIs (2 clinical trials; n=11,871) | no significant increase in VTE compared to controls |

SPECIAL POPULATIONS^{114,115,116,117,118,119,120,121}

Pediatrics

Safety and efficacy of the following agents in patients < 18 years of age have not been established: axitinib (Inlyta), cabozantinib (Cabometyx), lenvatinib (Lenvima), pazopanib (Votrient), sorafenib (Nexavar), sunitinib (Sutent), and tivozanib (Fotivda).

Everolimus (Afinitor) is FDA-approved in adults and children ≥ 1 year of age with SEGA associated with TSC who require therapeutic intervention but are not candidates for curative surgical resection.

In clinical trials, the incidence of serious infections was reported at a higher frequency in patients < 6 years of age taking everolimus.

Pregnancy

Pazopanib (Votrient), and sunitinib (Sutent) are all categorized as Pregnancy Category D. Women should be advised not to become pregnant while on therapy with any of these agents.

Based on findings from animal studies and their mechanisms' of action, axitinib (Inlyta), cabozantinib (Cabometyx), everolimus (Afinitor), lenvatinib (Lenvima), sorafenib (Nexavar), and tivozanib (Fotivda) can cause fetal harm when administered to pregnant women. When axitinib is used in combination with a checkpoint inhibitor, the prescribing information for either avelumab or pembrolizumab should be consulted for contraception and pregnancy information.

Women of childbearing potential should continue to use effective contraception during treatment and for varying lengths of time after the end of therapy. Some agents have specific recommendations, including axitinib (Inlyta), which recommends contraception use for 1 week after the last dose, everolimus (Afinitor), which recommends contraception use for up to 8 weeks after ending treatment, cabozantinib (Cabometyx), which recommends the continued use of effective contraception for 4 months after the final dose, pazopanib (Votrient), which advises patients to continue contraception use for at least 2 weeks after treatment (including those who have had vasectomies), sorafenib (Nexavar) which advises female patients to use contraception for 6 months following the last dose, and tivozanib which advises patients to continue contraception use for 1 month after the last dose.

Geriatrics

No difference in efficacy or safety between older and younger patients was observed with axitinib (Inlyta) either as single agent or when given in combination with either avelumab or pembrolizumab, cabozantinib (Cabometyx), lenvatinib (Lenvima), sorafenib (Nexavar), or tivozanib (Fotivda). No difference in safety between older and younger patients was observed with cabozantinib when given in combination with nivolumab. In a clinical trial, patients ≥ 65 years old receiving sunitinib for RCC, 16% versus 5% of patients experienced ≥ 3 adverse events in sunitinib compared with placebo, respectively.

In a randomized trial of advanced hormone receptor positive HER2-negative breast cancer patients, the incidence of deaths due to any cause within 28 days of the last everolimus (Afinitor) dose was 6% in patients ≥ 65 years of age compared to 2% in patients less than 65 years of age. Adverse reactions leading to permanent treatment discontinuation occurred in 33% of patients ≥ 65 years of age compared to 17% in patients less than 65 years of age.

In 2 other trials involving everolimus (Afinitor) (RCC, PNET), no overall differences in safety or effectiveness were observed between elderly and younger patients.

In the RCC trials, patients receiving pazopanib (Votrient) older than 60 years were at a greater risk for elevation of ALT (> 3 time the ULN). In the STS trials, patients older than 65 years of age had a higher incidence of grade 3 or 4 fatigue, hypertension, decreased appetite, and AST/ALT elevations compared to younger patients.

Renal Impairment

No initial dose adjustment is needed for patients receiving axitinib (Inlyta) with pre-existing mild to severe renal impairment. Caution should be used in patients with end-stage renal disease (estimated creatinine clearance [CrCl] < 15 mL/min) receiving axitinib (Inlyta).

Dosage adjustment of cabozantinib (Cabometyx) is not required in patients with mild or moderate renal impairment. There is no experience with cabozantinib (Cabometyx) in patients with severe renal impairment.

No clinical studies were conducted with everolimus (Afinitor) in patients with decreased renal function. Renal impairment is not expected to influence drug exposure, and no dosage adjustment is recommended in patients with renal impairment.

No dosage adjustment is required for patients with mild to moderate renal impairment receiving lenvatinib (Lenvima); however, the dose should be reduced in patients with severe renal impairment. Patients with RCC or EC and severe hepatic impairment should receive 10 mg daily while patients with DTC and severe hepatic impairment should receive 14 mg daily.

Patients with RCC and mild/moderate renal impairment were included in clinical trials of pazopanib (Votrient). Based on pharmacokinetic studies, renal impairment is not expected to influence pazopanib (Votrient) exposure, and dose adjustment is not necessary. Data are not available for patients with severe renal impairment or on dialysis receiving pazopanib (Votrient).

No sorafenib (Nexavar) dosage adjustments are necessary in patients with any degree of impaired renal function. However, the pharmacokinetics of sorafenib (Nexavar) has not been studied in patients who are receiving dialysis.

No adjustment to the starting dose is required with sunitinib (Sutent) in patients with mild, moderate, or severe renal impairment or in patients receiving hemodialysis. Subsequent dose modifications in patients with mild, moderate, or severe renal impairment should be based on safety and tolerability. Sunitinib (Sutent) exposure is 47% lower in subjects receiving hemodialysis; no initial dose adjustment is required, but subsequent doses in these patients may be increased gradually up to 2-fold based on safety and tolerability.

No dosage adjustment is required for tivozanib for patients with mild to severe renal impairment (CrCl, 15 to 89 mL/min). The dosage for end-stage renal disease (ESRD) has not been established.

Hepatic Impairment

For axitinib (Inlyta), no dose adjustment is recommended in mild hepatic impairment (Child-Pugh class A). The starting dose of axitinib (Inlyta) should be decreased by approximately half in patients with

moderate hepatic impairment (Child-Pugh class B). Axitinib (Inlyta) has not been studied in severe hepatic impairment (Child-Pugh class C).

The dose of cabozantinib (Cabometyx) should be reduced in patients with mild to moderate hepatic impairment (Child-Pugh class A or B). Cabozantinib (Cabometyx) is not recommended for use in patients with severe hepatic impairment.

For patients with SEGA who have severe hepatic impairment (Child-Pugh class C), the recommended starting dose of everolimus (Afinitor) is 2.5 mg/m² once daily. In this same population, patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment may not need an adjustment to the starting dose, but subsequent dosing should be based on therapeutic drug monitoring; adjust dose at 2-week intervals, as needed, to achieve and maintain trough concentrations of 5 to 15 ng/mL.

For other indications (RCC, PNET, Renal angiomyolipoma with TSC), the recommended dose of everolimus (Afinitor) for patients with mild hepatic impairment (Child-Pugh class A) is 7.5 mg daily and the dose may be decreased to 5 mg if not well tolerated. For moderate hepatic impairment (Child-Pugh class B), the recommended dose is 5 mg daily and the dose may be decreased to 2.5 mg if not well tolerated. In patients with severe hepatic impairment (Child-Pugh class C), if the desired benefit outweighs the risk, a dose of 2.5 mg may be used but must not be exceeded. Dose adjustments should be made if a patient's hepatic status changes during treatment.

No dose adjustment is recommended in patients receiving lenvatinib (Lenvima) who have mild or moderate hepatic impairment. In patients with severe hepatic impairment, the recommended dose is 14 mg once daily in the treatment of DTC and 10 mg once daily in the treatment of RCC or EC.

No dose adjustment is required in patients with mild hepatic impairment (either total bilirubin within normal limit with ALT > ULN or bilirubin > 1 to 1.5 times ULN regardless of ALT value) receiving pazopanib (Votrient). If an alternative is not possible in moderate hepatic impairment (total bilirubin > 1.5 times to 3 times ULN regardless of the ALT value), the dose of pazopanib (Votrient) should be reduced to 200 mg daily. Pazopanib (Votrient) is not recommended in severe hepatic impairment.

No dose adjustments are necessary in patients with mild to moderate hepatic impairment taking sorafenib (Nexavar), or sunitinib (Sutent); these agents have not been studied in patients with severe hepatic impairment. Cancer trials of sunitinib (Sutent) have excluded patients with ALT or AST > 2.5 times the ULN or, if due to liver metastases, greater than 5 times ULN. For sunitinib, hepatic function should be monitored and sunitinib should be interrupted for any grade 3 or 4 drug-related hepatic adverse events and discontinued if there is no resolution of the toxicity.

Dose adjustment of tivozanib is not required in mild hepatic impairment (Child-Pugh Class A); a reduction in dosage is recommended with moderate hepatic impairment (total bilirubin > 1.5 to 3 times ULN with any AST). The impact of severe hepatic impairment (Child-Pugh Class C) on tivozanib safety or effectiveness has not been determined.

Other Considerations

Axitinib (Inlyta) has not been studied in patients with evidence of untreated brain metastasis or recent active GI bleeding and should not be used in those patients due to the risk of hemorrhagic events.

Both female and male infertility may occur in patients receiving cabozantinib (Cabometyx), everolimus (Afinitor), and lenvatinib (Lenvima).

DOSAGES^{122,123,124,125,126,127,128,129}

| Drug | Dose | Administration Comments | Availability |
|---|---|--|---|
| axitinib (Inlyta) | <p>RCC as a single agent: 5 mg twice daily</p> <p>RCC in combination with avelumab: 5 mg twice daily with avelumab 800 mg IV every 2 weeks</p> <p>RCC in combination with pembrolizumab: 5 mg twice daily with pembrolizumab 200 mg IV every 3 weeks or 400 mg IV every 6 weeks</p> | Take with or without food; swallow whole with a glass of water | Tablets: 1 mg, 5 mg |
| cabozantinib (Cabometyx) | <p>RCC: 60 mg daily</p> <p>HCC: 60 mg daily</p> <p>RCC in combination with nivolumab: 40 mg daily with nivolumab 240 mg IV every 2 weeks or 480 mg IV every 4 weeks</p> | Do not administer with food; patients should not eat for 2 hours before and at least 1 hour after taking dose; swallow tablets whole, do not crush tablets | Tablets: 20 mg, 40 mg, 60 mg |
| everolimus (Afinitor, Afinitor Disperz) | <p>RCC: 10 mg daily</p> <p>SEGA: 4.5 mg/m² once daily. Subsequent titration to trough concentrations of 5 to 15 ng/mL</p> <p>Advanced NET: 10 mg daily</p> <p>PNET: 10 mg daily</p> <p>Renal angiomyolipoma with TSC: 10 mg daily</p> <p>Advanced HR+ Breast Cancer: 10 mg daily</p> <p>TSC-Associated Partial-Onset Seizures: 5 mg/m² once daily until disease progression or unacceptable toxicity</p> | <p>Tablets: May be taken consistently with or without food and should be swallowed whole with a glass of water</p> <p>Afinitor Disperz: Administer suspension immediately after preparation in either an oral syringe or small drinking glass; prepare suspension in water only; discard suspension if not administered within 60 minutes after preparation; Administer consistently at the same time every day consistently with or consistently without food; gloves should be worn to avoid possible contact with everolimus (Afinitor) when preparing suspensions of Afinitor Disperz for another person</p> | <p>Tablets: 2.5 mg, 5 mg, 7.5 mg, 10 mg tablets</p> <p>Afinitor Disperz tablets for oral suspension: 2 mg, 3 mg, 5 mg</p> <p>Do not combine the 2 dosage forms (Afinitor tablets and Afinitor Disperz tablets for suspension) to achieve desired total dose; use 1 dosage form or the other</p> |
| lenvatinib (Lenvima) | <p>DTC: 24 mg daily</p> <p>RCC: 18 mg daily in combination with everolimus 5 mg once daily</p> <p>HCC: 12 mg once daily actual body weight (≥ 60 kg); 8 mg once daily (actual body weight < 60 kg)</p> <p>EC: 20 mg daily in combination with pembrolizumab 200 mg IV infusion every 3 weeks</p> | Take with or without food; capsules should be swallowed whole or the whole capsule can be dissolved in a small glass of water or apple juice | <p>Capsules: 4 mg, 10 mg</p> <p>Capsules in packages containing a total daily dose of 8 mg, 10 mg, 14 mg, 18 mg, 20 mg, or 24 mg; 4 mg, 10 mg</p> |

DTC = differentiated thyroid carcinoma; EC = endometrial carcinoma; GIST = gastrointestinal stromal tumor; HCC = hepatocellular carcinoma; IV = intravenous; PNET = pancreatic neuroendocrine tumor; RCC = renal cell carcinoma; SEGA = subependymal giant cell astrocytoma

Dosages (continued)

| Drug | Dose | Administration Comments | Availability |
|----------------------|--|--|--|
| pazopanib (Votrient) | RCC: 800 mg daily Soft tissue sarcoma: 800 mg daily | Give at least 1 hour before or 2 hours after a meal; do not crush tablets; If a dose is missed, it should not be taken if it is less than 12 hours until the next dose | Tablets: 200 mg |
| sorafenib (Nexavar) | RCC: 400 mg twice daily HCC: 400 mg twice daily DTC: 400 mg twice daily | Take without food (at least 1 hour before or 2 hours after a meal) | Tablets: 200 mg |
| sunitinib (Sutent) | RCC: 50 mg daily; 4 weeks on therapy, 2 weeks off therapy RCC, adjuvant treatment: 50 mg daily; 4 weeks on therapy, 2 weeks off therapy for nine 6-week cycles GIST: 50 mg daily; 4 weeks on therapy, 2 weeks off therapy PNET: 37.5 mg once daily, continuously without a scheduled off-treatment period | May be taken with or without food | Capsules: 12.5 mg, 25 mg, 37.5 mg, 50 mg |
| tivozanib (Fotivda) | RCC: 1.34 mg orally once daily for 21 days on treatment followed by 7 days off treatment (28-day cycle) until disease progression or unacceptable toxicity | May be taken with or without food; capsules should be swallowed whole with a glass of water and should not be opened | Capsules: 0.89 mg, 1.34 mg |

DTC = differentiated thyroid carcinoma; EC = endometrial carcinoma; GIST = gastrointestinal stromal tumor; HCC = hepatocellular carcinoma; IV = intravenous; PNET = pancreatic neuroendocrine tumor; RCC = renal cell carcinoma; SEGA = subependymal giant cell astrocytoma

Dose escalation of axitinib when given in combination with avelumab beyond the initial 5 mg dose may be considered at intervals of 2 weeks or more.

Dose escalation of axitinib when given in combination with pembrolizumab beyond the initial 5 mg dose may be considered at intervals of 6 weeks or more.

Consult package insert for each individual medication for additional detailed information related to dosing and dose modifications due to adverse reactions and/or drug interactions, including recommendations for withholding or discontinuing both axitinib and either avelumab or pembrolizumab based on the development of hepatotoxicity with either combination.

Consult package insert for detailed instructions on preparation of Afinitor Disperz tablets for suspension in either an oral syringe or a small drinking glass.

CLINICAL TRIALS

Search Strategies

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled, comparative trials for FDA-approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Advanced HR+, HER-2 Negative Breast Cancer

everolimus (Afinitor) plus exemestane (Aromasin) versus exemestane plus placebo

BOLERO-2 was a phase 3, double-blind trial in which 724 patients with HR-positive, HER-2 negative advanced breast cancer were randomized to either everolimus plus exemestane (Aromasin) or exemestane plus placebo.¹³⁰ Eligible patients had either experienced a recurrence or progression of disease while receiving therapy with a nonsteroidal aromatase inhibitor either in the adjuvant setting or to treat advanced disease (or both). The primary endpoint of PFS was 6.9 months for everolimus plus exemestane versus 2.8 months for placebo plus exemestane according to local investigators (HR, 0.43; 95% confidence interval [CI], 0.35 to 0.54; $p < 0.001$) and 10.6 months versus 4.1 months, respectively, as assessed by a central review (HR, 0.36; 95% CI, 0.27 to 0.47; $p < 0.001$). Median overall survival (OS) was not statistically significantly different; 31 months in the exemestane plus everolimus arm and 26.6 months in the exemestane plus placebo arm (HR, 0.89; 95% CI, 0.73 to 1.1; $p = 0.14$).¹³¹ Additional treatments were received upon disease progression by 84% of patients in the combination arm and 90% of patients in the placebo arm. The most common grade 3 to 4 adverse events were stomatitis (8% versus 1%), anemia (6% versus less than 1%), dyspnea (4% versus 1%), hyperglycemia (4% versus less than 1%), fatigue (4% versus 1%), and pneumonitis (3% versus 0) in the exemestane-everolimus group compared to the exemestane-placebo group, respectively. The final PFS results with a median of 18 months follow up demonstrated a PFS of 7.8 months for the everolimus-exemestane arm versus 3.2 months for the placebo-exemestane arm by investigator review (HR, 0.45; 95% CI, 0.38 to 0.54; $p < 0.0001$) and 11 months versus 4.1 months, respectively, by central review (HR, 0.38; 95% CI, 0.31 to 0.48; $p < 0.0001$).¹³²

Differentiated Thyroid Carcinoma

lenvatinib (Lenvima) versus placebo

A randomized, double-blind, placebo-controlled, multicenter, phase 3 trial was conducted in 392 patients with locally recurrent or metastatic radioactive iodine-refractory differentiated thyroid cancer

and radiographic evidence of disease progression within 12 months prior to randomization.¹³³ Patients were randomized to lenvatinib 24 mg once daily (n=261) or placebo (n=131) until disease progression. The median treatment duration was 16.1 months for lenvatinib and 3.9 months for placebo. The major efficacy outcome measure was PFS. Secondary efficacy outcomes included objective response rate (ORR) and OS. The median cumulative radioactive iodine (RAI) activity administered prior to study entry was 350 mCi (12.95 GBq). A statistically significant prolongation in PFS was demonstrated with lenvatinib (18.3 months) versus placebo (3.6 months) (HR, 0.21; 95% CI, 0.16 to 0.28; p<0.001]). Upon confirmation of disease progression, 83% of patients in the placebo group crossed over to receive open-label lenvatinib. ORR was observed in 65% (partial response: 63%; complete response: 2%) and 2% (all partial responses) of patients in the lenvatinib and placebo groups, respectively (p<0.001). OS was not reached in either group. The most common adverse reactions for lenvatinib ($\geq 30\%$), in order of decreasing frequency: hypertension, fatigue, diarrhea, arthralgia/myalgia, decreased appetite, decreased weight, nausea, stomatitis, headache, vomiting, proteinuria, palmar-plantar erythrodysesthesia (PPE) syndrome, abdominal pain, and dysphonia. The most common serious adverse reactions were pneumonia (4%), hypertension (3%), and dehydration (3%). More patients in the lenvatinib arm had dose reductions because of adverse events compared to the placebo (68% versus 5%, respectively). A total of 14.2% of patients discontinued lenvatinib and 2.3% discontinued placebo due to adverse reactions. The most common adverse reactions that led to discontinuation of lenvatinib were hypertension and asthenia (1% each).

sorafenib (Nexavar) versus placebo

DECISION was a randomized, double-blind, placebo-controlled phase 3 trial in adult patients (n=417) comparing sorafenib 400 mg twice daily to placebo in patients with radioactive iodine-refractory locally-advanced or metastatic differentiated thyroid cancer.¹³⁴ Patients were required to have disease progression within 14 months prior to enrollment. The primary endpoint was PFS. Median PFS was significantly longer in the sorafenib group (10.8 months) than in the placebo group (5.8 months; HR, 0.59; 95% CI, 0.45 to 0.76; p<0.0001). Most adverse events in the sorafenib patients were grade 1 or 2 but, overall, 98.6% of patients receiving sorafenib experienced an adverse event. The most frequent adverse events associated with sorafenib included hand-foot skin reaction (76.3%), diarrhea (68.6%), alopecia (67.1%), and rash or desquamation (50.2%).

Endometrial Carcinoma (EC)

lenvatinib (Lenvima) plus pembrolizumab (Keytruda) – advanced disease

The efficacy of lenvatinib plus pembrolizumab was evaluated in a patient cohort with advanced endometrial cancer.¹³⁵ KEYNOTE-146/Study 111 is an ongoing open-label, multi-cohort, single-arm phase 1B/phase 2 study of patients with select solid tumors, including advanced endometrial carcinoma. Patients received lenvatinib 20 mg once daily orally in combination with pembrolizumab 200 mg IV once every 3 weeks. The primary endpoint was ORR at 24 weeks. Secondary endpoints included duration of response, PFS, and OS. Efficacy analyses included patients with endometrial carcinoma who previously received systemic treatment and completed 8 cycles of treatment (n=108). The ORR at 24 weeks was 38% (95% CI, 28.8 to 47.8). The median duration of response was 21.2 months (95% CI, 7.6 to not estimable), median PFS was 7.4 months (95% CI, 5.3 to 8.7), and median OS was 16.7 months (95% CI, 15 to not estimable).

Gastrointestinal Stromal Tumor (GIST)

sunitinib (Sutent) versus placebo

The efficacy and tolerability of sunitinib and placebo were compared in patients with advanced GIST who were resistant to or intolerant of prior treatment with imatinib.¹³⁶ In the double-blind, placebo-controlled, parallel-group, multicenter, phase 3 study, 312 patients were randomized to receive either sunitinib 50 mg once daily in 6-week cycles (4 weeks on and 2 weeks off) or placebo. The primary endpoint was time to tumor progression. Secondary endpoints were PFS, OS, and confirmed ORR. The median time to tumor progression was 27.3 weeks in the sunitinib treatment group and 6.4 weeks in the placebo group ($p < 0.0001$). Patients treated with sunitinib had a significantly longer duration of PFS (24.1 weeks versus 6 weeks; $p < 0.0001$) and significantly higher rate of confirmed objective response (7% versus 0%; $p = 0.006$) compared with those treated with placebo. Overall survival achieved with sunitinib prior to execution of the option to cross over was significantly better with sunitinib as compared to placebo (HR, 0.49; $p = 0.007$). Overall, sunitinib was well tolerated, with most adverse events being mild to moderate in severity. Fatigue, diarrhea, skin discoloration, and nausea were the more commonly experienced adverse effects in the sunitinib treatment group. Hematologic events appeared to be more prevalent in the sunitinib group.

Hepatocellular Carcinoma (HCC)

cabozantinib (Cabometyx) versus placebo – progressive disease

CELESTIAL was a randomized, double blind, multicenter, placebo-controlled, phase 3 trial involving 707 patients.¹³⁷ All patients had previously received sorafenib and had disease progression after at least 1 systemic treatment, and 27% of enrolled patients had received 2 prior systemic therapies for advanced HCC. Patients were randomized 2:1 to either cabozantinib 60 mg/day or placebo. The primary endpoint was OS with secondary endpoints including ORR and PFS. At the time of the planned second interim analysis with 484 deaths having occurred, the median OS was 10.2 months (95% CI, 9.1 to 12) for the cabozantinib group and 8 months (95% CI, 6.8 to 9.4) in the placebo group (HR, 0.76; 95% CI, 0.63 to 0.92; $p = 0.005$). The median ORR and PFS according to investigator assessed Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria, was 4% and 5.2 months (95% CI, 4 to 5.5), respectively, in the cabozantinib group and < 1% and 1.9 months (95% CI, 1.9 to 1.9), respectively, in the placebo group (HR, 0.44; 95% CI, 0.36 to 0.52; $p < 0.001$). Dose reductions occurred in 62% of cabozantinib-treated patients during a median duration of therapy of 3.8 months with 16% discontinuing the drug due to adverse events. The most common grade 3 to 4 adverse events versus placebo were palmar-plantar erythrodysesthesia (17% versus none, respectively), hypertension (16% versus 2%, respectively), increased AST level (12% versus 7%, respectively), fatigue (10% versus 4%, respectively), and diarrhea (10% versus 2%, respectively). There were 6 deaths considered to be related to cabozantinib.

lenvatinib (Lenvima) versus sorafenib (Nexavar)

An open-label, multicenter, phase 3, noninferiority trial randomized 954 treatment-naïve patients with unresectable HCC to either lenvatinib ($n = 478$) 8 mg/day or 12 mg/day based on body weight or sorafenib ($n = 476$) 400 mg twice daily.¹³⁸ The primary endpoint was OS. Median OS was 13.6 months (95% CI, 12.1 to 14.9) for lenvatinib and 12.3 months (95% CI, 10.4 to 13.9) for sorafenib which met the criteria for non-inferiority. OS superiority of lenvatinib compared to sorafenib was not achieved. The

most common adverse events for lenvatinib were hypertension (42%), diarrhea (39%), decreased appetite (34%), and decreased weight (31%), and for sorafenib, the most common adverse events were palmar-plantar erythrodysesthesia (52%), diarrhea (46%), hypertension (30%), and decreased appetite (27%).

sorafenib (Nexavar) versus placebo

SHARP: A randomized, double-blind, placebo-controlled, multicenter, phase 3 study of 602 patients with unresectable HCC compared sorafenib 400 mg twice daily to placebo.¹³⁹ The trial was stopped early for efficacy since sorafenib significantly prolonged OS (10.7 months compared with 7.9 months for sorafenib versus placebo, respectively; HR, 0.69; 95% CI, 0.55 to 0.87; $p < 0.001$). Improvement in OS was observed across patient subgroups. Based on independent radiologic review from an earlier time point than the survival analysis, time to tumor progression (TTP) was significantly longer compared to placebo in patients with advanced HCC (5.5 months versus 2.8 months for sorafenib and placebo, respectively; HR, 0.58; 95% CI, 0.45 to 0.74; $p < 0.001$). The disease control rate was significantly higher in the sorafenib group than in the placebo group (43% versus 32%; $p = 0.002$). Treatment-related adverse events were mostly grade 1 or 2, occurred early in treatment, and were medically manageable. Common side effects in the sorafenib group included diarrhea, weight loss, and hand-foot skin reaction. Subsequent subgroup analysis of the SHARP trial determined the improved median OS, the improved disease control rate, and the most common grade 3 to 4 adverse events were similar among all examined cohorts regardless of disease etiology, baseline tumor burden, performance status, tumor stage, and prior therapy.¹⁴⁰

Neuroendocrine Tumors of GI or Lung Origin

everolimus (Afinitor) versus placebo

RADIANT-4 was a phase 3, randomized, double-blind, placebo-controlled trial involving 302 adult patients with advanced, progressive, well-differentiated, non-functional neuroendocrine tumors of lung or GI origin.¹⁴¹ Patients were randomized to either everolimus 10 mg daily ($n = 205$) or placebo ($n = 97$) along with best supportive care. Patients were stratified by tumor origin, performance status, and previous treatment with somatostatin analogs. The primary endpoint was PFS as assessed by a central radiology review in the intent-to-treat (ITT) population. OS and health-related quality of life (HRQOL) were secondary endpoints. Median PFS was 11 months (95% CI, 9.2 to 13.3) in the everolimus group and 3.9 months (95% CI, 3.6 to 7.4) in the placebo group. Everolimus was associated with a 52% reduction in the estimated risk of progression or death (HR, 0.48; 95% CI, 0.35 to 0.67; $p < 0.00001$). At the first pre-planned interim analysis, OS was not statistically significantly different (HR, 0.64; 95% CI, 0.4 to 1.05; $p = 0.037$). Adverse effects that were grade 3 or 4 included stomatitis (9% versus 0%), diarrhea (7% versus 2%), infections (7% versus 0%), anemia (4% versus 1%), fatigue (3% versus 1%), and hyperglycemia (3% versus 0%) for everolimus and placebo, respectively. HRQOL was assessed using the Functional Assessment of Cancer Therapy-General (FACT-G) questionnaire at baseline then every 8 weeks for the first year and then every 12 weeks thereafter until study drug discontinuation.¹⁴² The HRQOL secondary endpoint was prespecified as the measure of time to definitive deterioration as demonstrated by a ≥ 7 point change in the FACT-G score in the intention to treat population. Median time to definitive deterioration in the FACT-G total score was 11.27 months with everolimus and 9.23 months with placebo (HR, 0.81; 95% CI, 0.55 to 1.21; $p = 0.31$). There was no relevant difference in HRQOL between the placebo group and the everolimus group. The authors suggested that given the

improved PFS with everolimus, this analysis indicated that HRQOL was preserved despite the usual toxic effects of everolimus.

Advanced Pancreatic Neuroendocrine Tumors (PNET)

everolimus (Afinitor) versus placebo

RADIANT-3:¹⁴³ A randomized, double-blind, multicenter trial compared everolimus 10 mg daily plus best supportive care (BSC) to placebo plus BSC in 410 patients with locally advanced or metastatic advanced PNET and disease progression within the previous 12 months. The primary endpoint was PFS evaluated by RECIST. Once radiological progression was documented, patients could be unblinded by the investigator; the placebo group was then able to receive open-label everolimus. Other endpoints included safety, ORR (complete response [CR] or partial response [PR]), response duration, OS. Crossover from placebo to open-label everolimus occurred in 73% of patients. This study showed a statistically significant improvement in PFS (median 11 months versus 4.6 months), resulting in a 65% risk reduction in investigator-determined PFS (HR, 0.35; 95% CI, 0.27 to 0.45; $p < 0.001$). For everolimus, investigator-determined response rate was low at 4.8% and there were no complete responses. The median OS results demonstrated no statistically significant treatment-related difference in OS (HR, 1.05; 95% CI, 0.71 to 1.55). The median exposure to everolimus was longer than exposure to placebo (38 weeks versus 16 weeks). Drug-related adverse events for everolimus versus placebo were mostly grade 1 or 2 and included stomatitis (64% versus 17%), rash (49% versus 10%), diarrhea (34% versus 10%), fatigue (31% versus 14%), and infections (23% versus 6%), which were primarily upper respiratory. Grade 3 or 4 events that occurred more frequently with everolimus compared to placebo were anemia (6% versus 0%) and hyperglycemia (5% versus 2%). The rates of treatment-emergent adverse events resulting in permanent discontinuation were 20% for everolimus versus 6% for placebo.

sunitinib (Sutent) versus placebo

A randomized, double-blind, placebo-controlled, phase 3 multicenter, international, trial compared sunitinib 37.5 mg once daily to placebo without a scheduled off-treatment period in patients ($n=171$) with unresectable PNET.¹⁴⁴ Patients were required to have documented RECIST-defined disease progression within the previous 12 months. The primary endpoint was PFS. Other endpoints included OS, ORR, and safety. As recommended by the Independent Data Monitoring Committee, the study was terminated prematurely prior to the pre-specified interim analysis due to more observed serious adverse events and deaths in the placebo group and a PFS favoring sunitinib. This may have led to an overestimate of the magnitude of PFS effect. Median investigator-assessed PFS for sunitinib and placebo at time of data cutoff were 10.2 and 5.4 months, respectively. There was a significant improvement in PFS for sunitinib (11.4%) over placebo (5.5%) as measured by both investigator and independent assessment (HR, 0.427; 95% CI, 0.26 to 0.66; $p < 0.001$). The ORRs were 9.3% and 0% in the sunitinib and placebo arms, respectively. OS data were not reported; however, there were 9 and 21 deaths with sunitinib (Sutent) and placebo, respectively at the time of study termination. The most frequent adverse events in the sunitinib group were diarrhea, nausea, vomiting, asthenia, fatigue, neutropenia, hypertension, and palmar-plantar erythrodysesthesia syndrome. Updated PFS results were published in February 2017. The new score was determined by results from retrospective blinded independent central reviews (BICR) of patient imaging. Ninety-four percent ($n=160$) of the original group completed their scans, which were utilized to calculate a median PFS of 12.6 (95% CI, 11.1 to

20.6) months for sunitinib and 5.8 (95% CI, 3.8 to 7.2) months for placebo (HR, 0.32; 95% CI, 0.18 to 0.55; p=0.000015).¹⁴⁵

Renal Angiomyolipoma with TSC

everolimus (Afinitor) versus placebo

EXIST-2: A randomized double-blind, placebo-controlled trial evaluated everolimus 10 mg/day in patients (n=118) with renal angiomyolipoma as a feature of TSC (n=113) or sporadic lymphangiomyomatosis (n=5) until disease progression or unacceptable toxicity.¹⁴⁶ The median duration of follow-up was 8.3 months (range, 0.7 to 24.8 months). The renal angiomyolipoma response rate (major efficacy outcome defined as $\geq 50\%$ reduction in angiomyolipoma volume, absence of new angiomyolipoma lesion ≥ 1 cm, absence of kidney volume increase $\geq 20\%$, and no angiomyolipoma related bleeding of \geq grade 2) was statistically significantly higher in everolimus patients; there were 42% (95% CI, 31 to 53) of patients with angiomyolipoma responses in the everolimus group versus 0% (95% CI, 0 to 9) in the placebo group (p<0.0001). The median response duration was 5.3 months (range, +2.3 to +19.6 months). There were 3 patients in the everolimus group and 8 patients in the placebo group with documented angiomyolipoma progression (secondary outcome) by central radiologic review. The time to angiomyolipoma progression was statistically significantly longer for everolimus (HR, 0.08; 95% CI, 0.02 to 0.37; p<0.0001). The skin lesion response rate (secondary outcome) was statistically significantly higher in for everolimus (26% versus 0%, p=0.0011); all skin lesion responses were partial responses. The most common adverse events in the everolimus and placebo groups, respectively, were stomatitis (48% versus 8%), nasopharyngitis (24% versus 31%), and acne-like skin lesions (22% versus 5%). Published results of an extension trial of EXIST-2 reported on patients who had a median duration of therapy with everolimus of 28.9 months.¹⁴⁷ The proportion of patients achieving angiomyolipoma reductions of $\geq 30\%$ and $\geq 50\%$ increased over time, reaching 81.6% and 64.5%, respectively by week 96. There were no incidences of renal bleeding. The long-term safety profile was consistent with previous reports and no new safety issues were identified and the frequency of emerging adverse events and serious adverse events lessened over time.

A subgroup analysis of the EXIST-1 trial (described below) examined the angiomyolipoma response rates seen in that study population via kidney CT or MRI screenings completed at baseline, as well as weeks 12, 24, 48, and annually thereafter.¹⁴⁸ Angiomyolipoma response rates were 53.3% and 0% for everolimus and placebo-treated patients, respectively.

Renal Cell Carcinoma (RCC)

axitinib (Inlyta) plus avelumab (Bavencio) versus sunitinib – first-line

JAVELIN Renal 101, a multicenter, randomized, open-label, phase 3 trial, compared axitinib plus avelumab to sunitinib in 886 randomized patients with previously untreated advanced RCC with a clear cell component.¹⁴⁹ Axitinib was dosed at 5 mg orally twice daily continuously, and avelumab was administered as 10 mg/kg IV every 2 weeks. Sunitinib was dosed at 50 mg orally once daily for 4 weeks of a 6-week cycle. Primary endpoints of the study were PFS, as assessed by a BICR utilizing RECIST v1.1, and OS among patients with PD-L1-positive tumors. Key secondary endpoints included PFS, assessed by BICR according to RECIST v1.1 and OS in the total population, irrespective of PD-L1 expression. A total of 560 patients (63.2%) had PD-L1 positive tumors and among this subgroup, median PFS was 13.8 months (95% CI, 11.1 to not estimable) for the axitinib plus avelumab group compared to 7.2 months

(95% CI, 5.7 to 9.7) in the sunitinib group (stratified HR for disease progression or death, 0.61; 95% CI, 0.47 to 0.79; $p < 0.001$). With a median follow up of 11.6 months, deaths from any cause occurred in 37 (13.7%) of avelumab plus axitinib-treated patients and in 44 (15.2%) of sunitinib-treated patients with a median follow up of 10.7 months (HR for death, 0.82; 95% CI, 0.53 to 1.28; $p = 0.38$). In the overall population, median PFS was 13.8 months (95% CI, 11.1 to not estimable) with axitinib plus avelumab compared to 8.4 months (95% CI, 6.9 to 11.1) with sunitinib (HR for disease progression or death, 0.69; 95% CI, 0.56 to 0.84; $p < 0.001$). Deaths from any cause were observed in 63 patients (14.3%) who received axitinib plus avelumab and in 75 patients (16.9%) who received sunitinib (HR for death, 0.78; 95% CI, 0.55 to 1.08; $p = 0.14$) with a median follow up of 12 months and 11.5 months, respectively. Diarrhea was the most common adverse event in both treatment groups, but there was a higher percentage of grade 3 or higher diarrhea in the axitinib plus avelumab group (6.7%) compared to the sunitinib group (2.7%). Incidence of grade 3 or higher adverse events occurred in similar numbers of patients (309 [71.2%] of patients treated with axitinib plus avelumab and in 314 [71.5%]) of patients treated with sunitinib. Adverse events that led to treatment discontinuation occurred in 7.6% of patients in the axitinib plus avelumab arm and 13.4% of patients in the sunitinib arm. There were 3 deaths attributed to toxicity in the avelumab plus axitinib group (sudden death, myocarditis and necrotizing pancreatitis) and 1 in the sunitinib group (intestinal perforation). The most frequent immune-related adverse events occurring in the axitinib plus avelumab group were immune-related thyroid disorders in 107 (24.7%) of patients. A total of 39 (9%) of patients had grade 3 or higher immune-related adverse events.

axitinib (Inlyta) plus pembrolizumab (Keytruda) versus sunitinib – first-line

KEYNOTE-426 was a phase 3, randomized, open-label trial that included 861 patients with previously untreated advanced clear-cell renal carcinoma.¹⁵⁰ Patients were randomized to receive axitinib 5 mg orally twice daily plus pembrolizumab 200 mg IV every 3 weeks or sunitinib 50 mg orally once daily for 4 weeks of each 6-week cycle. The primary endpoints were PFS and OS as assessed by a BICR according to RECIST v1.1 in the ITT population. After a median follow up of 12.8 months, median PFS was 15.1 months in the axitinib plus pembrolizumab group and 11.1 months in the sunitinib group (HR for disease progression or death, 0.69; 95% CI, 0.57 to 0.84; $p < 0.001$). The median OS was not reached in either group. The percentage of patients alive at 12 months was 89.9% (95% CI, 86.4 to 92.4) in the axitinib plus pembrolizumab group and 78.3% (95% CI, 73.8 to 82.1) in the sunitinib group (HR for death, 0.53; 95% CI, 0.38 to 0.74; $p < 0.0001$). Grade 3 or higher adverse events occurred in 75.8% of the axitinib plus pembrolizumab group compared to 70.6% in the sunitinib group. The most common adverse events were diarrhea and hypertension. There were 4 deaths from treatment-related adverse events in the axitinib plus pembrolizumab group (myasthenia gravis, myocarditis, necrotizing fasciitis and pneumonitis) and 7 treatment-related deaths in the sunitinib group (acute myocardial infarction, cardiac arrest, fulminant hepatitis, GI hemorrhage, intracranial hemorrhage, malignant neoplasm progression, and pneumonia). The most common reason for treatment discontinuation was disease progression.

axitinib (Inlyta) versus sorafenib (Nexavar) – progressive disease

The AXIS trial evaluated the safety and efficacy of axitinib for advanced RCC in a randomized, open-label, multicenter, phase 3 study ($n = 723$).¹⁵¹ Patients were required to have had disease progression on or after treatment with 1 prior therapy, including sunitinib, bevacizumab, temsirolimus, or cytokine-containing regimens (interleukin-2 or interferon-alfa), and were randomized 1:1 to axitinib 5 mg twice

daily (n=361) or sorafenib 400 mg twice daily (n=362). The median duration of treatment was 6.4 months for axitinib and 5 months for sorafenib. PFS was evaluated by a BICR committee. Median PFS, the primary endpoint, was 6.7 months for axitinib versus 4.7 months for sorafenib (HR, 0.67; 95% CI, 0.54 to 0.81; 1-sided p<0.0001). The difference between the arms in the endpoint for OS was not statistically significant. The ORR was 19.4% for axitinib and 9.4% for sorafenib. Treatment discontinuation due to toxic reactions was 4% versus 8% for axitinib versus sorafenib, respectively. Updated results of the AXIS trial demonstrated an improvement in PFS (8.3 months for axitinib versus 5.7 months for sorafenib; HR, 0.656 [95% CI, 0.552 to 0.779]; p<0.0001) but no difference in OS (20.1 months versus 19.2 months; HR, 0.969 [95% CI, 0.8 to 1.174]; p=0.3744).¹⁵² A subsequent sub-group analysis revealed that, although longer duration of first-line therapy did generally lead to better outcomes with second-line therapy, the lack of response to first-line therapy did not preclude a positive response with a second-line agent.¹⁵³

cabozantinib (Cabometyx) versus everolimus (Afinitor) – progressive disease

METEOR: A multicenter, randomized, open-label, phase 3 trial compared cabozantinib to everolimus in patients with advanced RCC (Karnofsky Performance Score \geq 70%) who had received at least 1 prior anti-angiogenic therapy.¹⁵⁴ Patients were stratified by the number of prior VEGF tyrosine kinase inhibitors (TKIs) and by Memorial Sloan Kettering Cancer Center (MSKCC) Risk Group (n=658). Patients were randomized to cabozantinib 60 mg or everolimus 10 mg daily. Treatment continued until disease progression or unacceptable toxicity, and assessments occurred every 8 weeks during the first year and every 12 weeks thereafter. The primary outcome was PFS (assessed by a blinded review committee) for the first 375 patients randomized. Other efficacy endpoints included OS and ORR in the ITT population. The majority of those included were male and had received only 1 prior anti-angiogenic therapy; median age was 62 years. Median PFS was 7.4 months (95% CI, 5.6 to 9.1) with cabozantinib and 3.8 months (95% CI, 3.7 to 5.4) with everolimus (HR, 0.58; 95% CI, 0.45 to 0.75; p<0.0001). ORR occurred in 21% of patients randomized to cabozantinib and 5% of patients randomized to everolimus (p<0.001). Final median OS was 21.4 months (95% CI, 18.7 to not estimable) with cabozantinib and 16.5 months (95% CI, 14.7 to 18.8) with everolimus (HR, 0.66; 95% CI, 0.53 to 0.83; p=0.00026).¹⁵⁵ Adverse effects occurred in nearly all patients; however, discontinuations due to adverse effects were comparable in both groups (9% with cabozantinib, 10% with everolimus). The most common grade 3 or 4 adverse events were hypertension (15% versus 4%), diarrhea (13% versus 2%), fatigue (11% versus 7%), palmar-plantar erythrodysesthesia syndrome (8% versus 3%), anemia (6% versus 17%), hyperglycemia (1% versus 5% and hypomagnesemia (5% versus 0%) in the cabozantinib and everolimus groups, respectively. A subsequent subgroup analysis of the METEOR trial evaluated ORR, PFS, and OS by prior therapy received, including sunitinib, pazopanib, or a programmed death (PD)-1/programmed death ligand (PD-L1) inhibitor as the first-line agent for mRCC. Cabozantinib was found to be associated with better outcomes than everolimus in the second line setting, regardless of which therapy had been given in the first-line setting.¹⁵⁶ A follow up evaluation of quality of life (QOL) outcomes from the METEOR trial found that there was no overall difference demonstrated over time between the 2 groups in either of the 2 instruments utilized to measure QOL. The cabozantinib arm was associated with worse diarrhea and nausea while the everolimus arm was associated with worse shortness of breath. Cabozantinib improved time to deterioration overall (defined as the earlier date of death, radiographic progressive disease, or a \geq 4-point decrease from baseline in QOL scoring). In particular, patients with bone metastases had a markedly improved TDD from baseline with cabozantinib.¹⁵⁷

cabozantinib (Cabometyx) versus sunitinib (Sutent) – initial therapy

CABOSUN: A randomized phase 2 multicenter trial compared cabozantinib and sunitinib in the setting of first-line therapy in patients with metastatic RCC.¹⁵⁸ Participants were required to have untreated clear cell metastatic RCC, an Eastern Cooperative Oncology Group performance status of 0 to 2 and in intermediate or poor risk per International Metastatic Renal Cell Carcinoma Database Consortium criteria. Patients were randomly assigned to one of two groups: cabozantinib 60 mg once daily (n=79) or sunitinib 50 mg once daily with 4 weeks on and 2 weeks off (n=78). The primary endpoint, PFS, was measured from data obtained from July 2013 to April 2015. Treatment with cabozantinib had a greater median PFS in comparison to sunitinib (8.2 and 5.6 months, respectively). Incidence of grade 3 or 4 adverse events were similar between the 2 groups (67% for cabozantinib and 68% for sunitinib), with diarrhea, fatigue, and hypertension occurring in both groups. An updated analysis of ORR, OS, and PFS by an independent review committee (IRC) reported the ORR was 20% (95% CI, 12 to 30.8) for cabozantinib versus 9% (95% CI, 3.7 to 17.6) for sunitinib. The IRC assessed PFS was 8.6 months (95% CI, 6.8 to 14) versus 5.3 months (95% CI, 3 to 8.2) for cabozantinib versus sunitinib, respectively (HR, 0.48; 95% CI, 0.31 to 0.74; p=0.0008). With a median follow up of 35.4 months, the median OS was 26.6 months (95% CI, 14.6 to not estimable) with cabozantinib and 21.2 months (95% CI, 16.3 to 27.4) with sunitinib (HR, 0.8; 95% CI, 0.53 to 1.21). The updated incidence of grade 3 or 4 adverse events was 68% for cabozantinib and 65% for sunitinib.¹⁵⁹

cabozantinib (Cabometyx) plus nivolumab (Opdivo) versus sunitinib (Sutent) – initial therapy

CHECKMATE-9ER: A phase 3, randomized (1:1), open-label trial compared nivolumab 240 mg IV every 2 weeks combined with cabozantinib 40 mg once daily (n=323) and sunitinib 50 mg once daily for 4 weeks and off 2 weeks of each 6 week cycle (n=328) in the setting of first-line therapy in previously untreated patients with metastatic RCC.¹⁶⁰ The primary outcome, PFS, was assessed using RECIST v.1.1 by BICR. The median PFS for nivolumab plus cabozantinib compared with sunitinib was 16.6 months (95% CI, 12.5 to 24.9) and 8.3 months (95% CI, 7 to 9.7), respectively, with a median follow-up for OS of 18.1 months (range, 10.6 to 30.6). The probability of PFS at 12 months was superior in nivolumab plus cabozantinib compared with sunitinib; 57.6% (95% CI, 51.7 to 63.1) and 36.9% (95% CI, 31.1 to 42.8), respectively (HR, 0.51; 95% CI, 0.41 to 0.64; p<0.001). The probability of overall survival at 12 months was significant for nivolumab plus cabozantinib compared with sunitinib, 85.7% (95% CI, 81.3 to 89.1; p=0.001) and 75.6% (95% CI, 70.5 to 80), respectively, (HR, 0.6; 98.89% CI, 0.4 to 0.89; p=0.001). Neither group reached median overall survival. Objective response in nivolumab plus cabozantinib compared with sunitinib was 55.6% (95% CI, 50.1 to 61.2) and 27.1% (95% CI, 22.4 to 32.3; p<0.001). A complete response was observed in 8% and 4.6% of patients in the nivolumab plus cabozantinib and sunitinib groups, respectively. The median time to response was 2.8 months and 4.2 months with a median duration of response of 20.2 months and 11.5 months in the nivolumab plus cabozantinib and sunitinib groups, respectively. Adverse events grade ≥ 3 occurred in 75.3% and 70.6% of patients who received nivolumab plus cabozantinib and sunitinib, respectively.

everolimus (Afinitor) versus placebo – progressive disease

RECORD-1: A randomized, double-blind multicenter trial comparing everolimus 10 mg daily and placebo, both in conjunction with best supportive care, was conducted in 416 patients with metastatic RCC whose disease had progressed despite prior treatment with sunitinib, sorafenib, or both sequentially.¹⁶¹ Prior therapy with bevacizumab, interleukin-2, or interferon-α was also permitted. PFS, documented using RECIST, was assessed via blinded, independent, central radiologic review. After

documented radiological progression, patients could be unblinded by the investigator; those randomized to placebo were then able to receive open-label everolimus 10 mg daily. Everolimus was superior to placebo for PFS (4.9 months to 1.9 months, respectively; $p < 0.0001$). The mean OS was 14.8 months versus 14.4 months for everolimus versus placebo, respectively, $p = 0.162$, with 80% of patients in the placebo arm crossed over to everolimus.¹⁶² Using the rank-preserving structural failure time model, the survival corrected for crossover was 1.9-fold longer (95% CI, 0.5 to 8.5) with everolimus versus placebo. The treatment effect was similar across prognostic scores and prior sunitinib and/or sorafenib use.

lenvatinib (Lenvima) versus everolimus (Afinitor) versus lenvatinib (Lenvima) plus everolimus (Afinitor) – progressive disease

A phase 2, multicenter, open-label trial compared lenvatinib (24 mg/day) to everolimus (10 mg/day) or the combination of both drugs (lenvatinib 18 mg/day plus everolimus 5 mg/day) in 153 patients with advanced or metastatic clear cell RCC.¹⁶³ All patients had previously been treated with 1 VEGF-targeted therapy and had progressed either on therapy or within 9 months of stopping therapy. Based on investigator-assessed responses, lenvatinib plus everolimus significantly prolonged PFS (the primary endpoint) compared with everolimus alone (median, 14.6 months versus 5.5 months [HR, 0.4; 95% CI, 0.24 to 0.68; $p = 0.0005$]) but not compared to lenvatinib alone (14.6 months versus 7.4 months [HR, 0.66; 95% CI, 0.3 to 1.1; $p = 0.12$]). When single-agent lenvatinib was compared to single-agent everolimus by investigator review, there was a significant improvement in PFS favoring lenvatinib (HR, 0.61; 95% CI, 0.38 to 0.98; $p = 0.048$). An ad hoc, retrospective review of the data was conducted by a blinded, independent radiologic review (IRR) at the request of regulatory authorities. The retrospective IRR examined 86 progression events compared to the 101 events reported in the primary analysis.¹⁶⁴ Median PFS by IRR was 12.8 months (95% CI, 7.4 to 17.5) in the combination therapy arm, 9 months (95% CI, 5.6 to 10.2) in the lenvatinib alone arm, and 5.6 months (95% CI, 3.6 to 9.3) in the everolimus alone arm. PFS was significantly longer in the lenvatinib plus everolimus group than in the everolimus alone group (HR, 0.45; 95% CI, 0.27-0.79; $p = 0.0029$). In contrast to the investigator-assessed PFS, the IRR found no significant difference in PFS between the lenvatinib only versus the everolimus only groups (HR, 0.62; 95% CI, 0.37 to 1.04; $p = 0.12$). grade 3 and 4 adverse events were more common in the lenvatinib monotherapy arm (79%) compared to the everolimus alone arm (50%) or the combination therapy arm (71%). The most common grade 3 to 4 events were anemia associated with everolimus, proteinuria associated with single agent lenvatinib, and diarrhea associated with the combination arm. Two deaths were considered related to the study drug, 1 cerebral hemorrhage in the combination arm and 1 myocardial infarction in a patient receiving single-agent lenvatinib.

pazopanib (Votrient) versus sunitinib (Sutent) – first-line

COMPARZ: The efficacy and safety of pazopanib were studied in comparison to sunitinib in the first-line setting for RCC.¹⁶⁵ The open-label, phase 3 trial enrolled 1,110 patients with clear-cell, metastatic RCC and randomized them to either pazopanib 800 mg daily given continuously or sunitinib given as 50 mg daily for 4 weeks followed by 2 weeks without treatment. Primary endpoint was PFS and secondary endpoints were OS, safety, and quality of life. The study was powered to show noninferiority of pazopanib compared to sunitinib. Pazopanib was noninferior to sunitinib with respect to PFS (HR for progression of disease or death from any cause, 1.05; 95% CI, 0.9 to 1.22; p -value not reported), meeting the predefined noninferiority margin (upper bound of the 95% CI, < 1.25). Overall survival at time of study publication was similar (HR for death with pazopanib, 0.91; 95% CI, 0.76 to 18). Patients

treated with sunitinib, as compared with those treated with pazopanib, had a higher incidence of fatigue (63% versus 55%), hand-foot syndrome (50% versus 29%), and thrombocytopenia (78% versus 41%); patients treated with pazopanib had a higher incidence of alopecia, weight loss, and increased levels of alanine aminotransferase (60% versus 43% with sunitinib). The proportion of patients who discontinued the study drug because of adverse events was 24% in the pazopanib group and 20% in the sunitinib group; the higher discontinuation rate observed for pazopanib was primarily due to abnormalities in liver-function tests (6% versus 1%). Analyses of health-related quality of life showed that patients who received pazopanib reported less fatigue, fewer side effects, such as soreness of the hand or foot and soreness of the mouth or throat, and better satisfaction with treatment than did those who received sunitinib. Notably, QOL measurements were taken at day 28, prior to the 2 weeks of no treatment with sunitinib in a 42-day cycle. A subsequently published final analysis of overall survival showed similar results between the 2 groups (HR, 0.92; 95% CI, 0.79 to 1.06; $p=0.24$), as well as OS between the stratified risk groups, supporting the findings of the primary analysis of noninferiority of pazopanib versus sunitinib as first-line treatment for clear cell RCC.¹⁶⁶

pazopanib (Votrient) versus sunitinib (Sutent) – quality of life

PISCES: A randomized, double-blind, cross-over trial assessed the patient reported treatment preference for pazopanib versus sunitinib in patients with metastatic RCC.¹⁶⁷ Patients ($n=169$) were randomly assigned to pazopanib 800 mg daily for 10 weeks followed by a 2-week washout period and then sunitinib 50 mg daily (4 weeks on, 2 weeks off every 6 week cycle) for 10 weeks or the reverse sequence. The primary endpoint was assessed by questionnaire regarding patient preference for a specific treatment at the end of the 2 treatment periods. Other endpoints analyzed included reasons for patient preference, physician preference, safety, and HRQOL. Significantly more of the 114 patients analyzed in the modified intention-to-treat criteria preferred pazopanib (70%) over sunitinib (22%), while 8% expressed no preference ($p<0.001$). Less fatigue and better quality of life were the main reasons for preferring pazopanib, while less diarrhea was the most frequently cited reason among those patients who preferred sunitinib. Physicians also preferred pazopanib (61%) over sunitinib (22%), while 17% of physicians expressed no preference. Pazopanib was superior to sunitinib in HRQOL measures evaluating fatigue, hand/foot soreness, and mouth/throat soreness.

sorafenib (Nexavar) versus placebo – progressive disease

TARGET: A phase 3, randomized, double-blind, placebo-controlled trial evaluated the effect of sorafenib 400 mg twice daily on PFS and OS in 903 patients with advanced RCC who had failed previous systemic therapy.¹⁶⁸ The median PFS survival for sorafenib patients was 5.5 months versus 2.8 months for placebo patients. Sorafenib was associated with a 56% reduction in the risk of progression versus placebo (HR, 0.44; 95% CI, 0.35 to 0.55, $p<0.001$). Due to the significant improvement in PFS, placebo patients were allowed to cross over to sorafenib. Median OS was not significant in the intent-to treat population, 17.8 months for sorafenib versus 15.2 months for placebo assigned patients (HR, 0.88; $p=0.146$). However, after the patients who crossed over to sorafenib were censored, the OS difference reached statistical significance of 17.8 months versus 14.3 months (HR, 0.78; $p=0.029$).¹⁶⁹ Treatment-related adverse events were predominantly grade 1 or 2. The most common adverse events were diarrhea, rash, fatigue, hand-foot skin reactions, alopecia, and nausea. A total of 169 sorafenib-treated patients received treatment for more than 1 year; 27 patients received treatment for over 2 years. Long-term treatment with sorafenib was not associated with any new or unexpected toxicity.¹⁷⁰

sorafenib (Nexavar) versus axitinib (Inlyta) – first-line treatment

Sorafenib (Nexavar) was compared to axitinib (Inlyta) in the first-line setting of treatment-naïve patients with metastatic clear cell RCC.¹⁷¹ This was a randomized, open-label, phase 3 trial looking at PFS as the primary endpoint. A total of 192 treatment-naïve patients received axitinib and 96 treatment-naïve patients received sorafenib. There was no significant difference between the 2 groups for median PFS (10.1 months for axitinib [95% CI, 7.2 to 12.1] versus 6.5 months for sorafenib [95% CI, 4.7 to 8.3]; HR, 0.77; 95% CI, 0.56 to 1.05). Diarrhea, hypertension, weight decrease, decreased appetite, dysphonia, hypothyroidism, and upper abdominal pain were more common with axitinib while hand foot syndrome, rash, alopecia, and erythema were more common with sorafenib. Serious adverse events were reported in 34% of patients receiving axitinib and 25% of patients receiving sorafenib. Median OS was 21.7 months (95% CI, 18 to 31.7) with axitinib versus 23.3 months (95% CI, 18.1 to 33.2) with sorafenib (HR, 0.995; 95% CI, 0.731 to 1.356; $p=0.4883$).¹⁷²

sunitinib (Sutent) versus interferon alpha – first-line

A randomized, multicenter, phase 3 study of 750 patients with previously untreated, metastatic RCC received either repeated 6-week cycles of sunitinib (Sutent) (at a dose of 50 mg given orally once daily for 4 weeks, followed by 2 weeks without treatment) or interferon-alfa (at a dose of 9 million units [MU] given subcutaneously [SC] 3 times weekly).¹⁷³ Interferon alfa was standard of care at the time of the study. The median PFS was significantly longer in the sunitinib group (11 months) than in the interferon-alfa group (5 months), corresponding to a HR of 0.42 (95% CI, 0.32 to 0.54; $p<0.001$). Sunitinib was also associated with a higher objective response rate (secondary endpoint) than was interferon alfa (31% compared with 6%, $p<0.001$). The proportion of patients with grade 3 or 4 treatment-related fatigue was significantly higher in the group treated with interferon-alfa. Diarrhea was more common in the sunitinib group ($p<0.05$). Follow-up showed that sunitinib had longer overall survival compared with interferon alfa. Median OS (26.4 versus 21.8 months, respectively; HR, 0.821; 95% CI, 0.673 to 1.01; $p=0.051$) per the primary analysis of unstratified log-rank test ($p=0.013$ per unstratified Wilcoxon test).¹⁷⁴ By stratified log-rank test, the HR was 0.818 (95% CI, 0.669 to 0.999; $p=0.049$). Within the interferon group, 33% of patients received sunitinib and 32% received other vascular endothelial growth factor (VEGF)-signaling inhibitors after discontinuation from the trial.

sunitinib (Sutent) versus placebo – adjuvant therapy

ASSURE was a randomized, double blind, phase 3 trial that examined the role of adjuvant sunitinib in RCC patients who had undergone nephrectomy and were at a high risk of disease recurrence.¹⁷⁵ Patients ($n=615$) with locoregional clear cell RCC who underwent nephrectomy were randomized 1:1 to receive either sunitinib or placebo. Sunitinib/placebo was dosed as 50 mg/day for a 4 weeks-on, 2 weeks off schedule for 1 year or until disease recurrence, unacceptable toxicity, or consent withdrawal. The primary endpoint was disease-free survival according to a BICR. Secondary endpoints included investigator-assessed disease-free survival, overall survival, and safety. The median duration of disease-free survival was 6.8 years (95% CI, 5.8 to not reached) in the sunitinib group and 5.6 years (95% CI, 3.8 to 6.6) in the placebo group (HR, 0.76; 95% CI, 0.59 to 0.98; $p=0.03$). Dose reductions, dose interruptions, and dose discontinuations due to adverse events as well as grade 3 or 4 adverse events were all more common in the sunitinib group compared to the placebo group. The most common adverse events in the sunitinib-treated cohort that were attributed to treatment by the investigators were diarrhea, palmar-plantar erythrodysesthesia, fatigue, hypertension, and mucosal inflammation.

tivozanib (Fotivda) versus sorafenib (Nexavar)

TIVO-3: A phase 3, randomized, controlled, open-label, multicenter, multinational, parallel-arm study evaluated tivozanib versus sorafenib (Nexavar) in patients with relapsed or refractory advanced RCC who received 2 or 3 prior systemic treatments including ≥ 1 VEGFR kinase inhibitor other than sorafenib or tivozanib.¹⁷⁶ Patients (n=350) were stratified based on prior therapies: 2 kinase inhibitors (45%), kinase inhibitor plus immune checkpoint inhibitor (programmed death receptor-1 [PD-1] or programmed death ligand 1 [PD-L1]) (26%), or kinase inhibitor plus other systemic agent (29%), as well as by International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic score. Patients were randomized 1:1 to tivozanib (n=175) 1.34 mg orally once daily for 21 days, off 7 days for a 28-day cycle or sorafenib (n=175) 400 mg orally twice daily continuously, until disease progression or toxicity. Median follow-up was 19 months (interquartile range [IQR], 15 to 23.4). PFS events occurred in both tivozanib and sorafenib patients (70%); tivozanib was found to have a significantly longer PFS compared to sorafenib (HR, 0.73; 95% CI, 0.56 to 0.94; p=0.016), with a median PFS of 5.6 months (95% CI, 5.29 to 7.33) versus 3.9 months (95% CI, 3.71 to 5.55). Median overall survival was shorter in tivozanib-treated patients compared to sorafenib patients (HR, 0.99; 95% CI, 0.76 to 1.29) with a median OS of 16.4 months (95% CI, 13.4 to 22.2) and 19.7 months (95% CI, 15 to 24.2), respectively. Of the patients with measurable disease at baseline, tivozanib (18%; 95% CI, 12 to 24) demonstrated a higher ORR than sorafenib (8%; 95% CI, 4 to 13). The duration of response in months was not reached (NR) for tivozanib-treated patients (95% CI, 12.9 to NR) versus 5.7 months (95% CI, 5.6 to NR) for sorafenib-treated patients.

Soft Tissue Sarcoma (STS)

pazopanib (Votrient) versus placebo

PALETTE:¹⁷⁷ The safety and efficacy of pazopanib (800 mg once daily) in patients with STS were evaluated in a randomized, double-blind, placebo-controlled, multicenter trial (n=369) with metastatic STS who had failed at least 1 prior anthracycline-based chemotherapy. Patients with GIST or adipocytic sarcoma were excluded. The median duration of treatment was 4.5 months for patients on the pazopanib arm and 1.9 months for patients on the placebo arm. Secondary efficacy endpoints included OS, overall response rate, and duration of response. Overall intention-to-treat PFS (primary endpoint) was 4.6 versus 1.6 months, for pazopanib (Votrient) versus placebo, respectively (HR, 0.31; 95% CI, 0.24 to 0.4; p<0.001). Median OS was 12.5 months for patients randomized to pazopanib and 10.7 months for placebo (HR, 0.86; 95% CI, 0.67 to 1.11; p=0.25). The most common adverse events were fatigue (placebo 49% versus pazopanib 65%), diarrhea (16% versus 58%), nausea (28% versus 54%), weight loss (20% versus 48%), and hypertension (7% versus 41%).

Subependymal Giant Cell Astrocytoma with Tuberous Sclerosis Complex (SEGA)

everolimus (Afinitor) versus placebo

The EXIST-1 trial, a phase 3 multicenter, double blind, placebo-controlled trial, randomized 117 pediatric and adult patients (median age 9.5 years) with SEGA and TSC to everolimus 4.5 mg/m² daily or placebo.¹⁷⁸ MRI scans were obtained at baseline and at scheduled intervals thereafter to assess the response rate. Response was defined as $\geq 50\%$ reduction in the sum of SEGA volume relative to baseline in the absence of unequivocal worsening of non-target SEGA lesions, a new SEGA lesion ≥ 1 centimeter, and new or worsening hydrocephalus. The response rate was statistically significantly

higher in the everolimus-treated patients; there were 27 (35%) patients with response in the everolimus arm and no responses in the placebo arm ($p < 0.0001$). With a median follow-up of 8.4 months, SEGA progression was detected in 6 of 39 (15.4%) patients randomized to placebo and none of the 78 patients randomized to everolimus (Afinitor). An open-label, 4-year extension trial of the EXIST-1 trial involved 111 of the 117 originally randomized patients (including patients initially randomized to everolimus and those who crossed over to everolimus from placebo for the extension phase of the study).¹⁷⁹ Using the same response criteria, at a median follow up of 28.3 months, the response rates were 37% in 105 patients at 24 weeks, 46% in 104 patients at 48 weeks, 47% in 76 patients at 96 weeks. Duration of response ranged from 2.1 months to 31.1 months (median not reached). Stomatitis (43%) and mouth ulceration (30%) were the most frequent treatment-related adverse events while infections were the most common treatment-related serious adverse event, occurring in 14% of patients.

A *post hoc* analysis of safety data in a subgroup of 18 patients less than 3 years old was conducted.¹⁸⁰ The median age of this group was 1.82 years. Adverse events were reported in all patients with 67% experiencing grade 3 events and 11% experiencing grade 4 events. One patient discontinued treatment secondary to adverse events (bacteremia, viral infection, and increased blood alkaline phosphatase). The most common adverse events were stomatitis, cough, pharyngitis, and pyrexia, but no new safety issues were identified in this population.

everolimus (Afinitor) in pediatrics

A prospective, open-label, single-arm trial evaluated the safety and efficacy of everolimus (Afinitor) in patients with SEGA associated with TSC.^{181, 182} A total of 28 patients received everolimus (Afinitor). The median age was 11 years (range 3 to 34 years). The median duration of treatment was 24.4 months. At 6 months, 32% of patients (95% CI, 16 to 52) experienced at least a 50% reduction in the tumor volume of their largest SEGA lesion; 75% of patients had at least a 30% reduction. Duration of response for these patients ranged from 97 to 946 days (median 266 days). None of the patients developed a new lesion, worsening hydrocephalus, increased intracranial pressure, required surgical resection, or other therapy for SEGA while receiving everolimus (Afinitor). A total of 16 patients had 24-hour video electroencephalography. In these patients, seizure frequency decreased in 9 patients, did not change in 6 patients, and increased in 1 patient (median change, -1 seizure; $p = 0.02$). The most common adverse events were stomatitis (86%) and upper respiratory infections (82%).

Tuberous Sclerosis Complex (TSC)-Associated Partial-Onset Seizures

sunitinib (Sutent) versus placebo

A phase 3, randomized, double blind, placebo-controlled, multicenter study enrolled 366 patients between the ages of 2 and 65 years with TSC and treatment-resistant seizures.¹⁸³ Patients were required to have a history of inadequate control of partial-onset seizures despite treatment with ≥ 2 antiepileptic drug (AED) regimens. Additional inclusion criteria included a minimum of 16 partial-onset seizures during the initial 8-week baseline phase of the study. Initial doses were weight-based and were adjusted based on the whether or not the patient was receiving concomitant CYP3A4 inducing drugs. Dose adjustments were then done to maintain prespecified target trough ranges throughout the study (a low exposure group and a high exposure group). The primary endpoint was change from baseline in the frequency of seizures during the 12-week maintenance phase. The response rates were 15.1% with placebo and 28.2% for low-exposure everolimus and 40% for high-exposure everolimus.

The median percentage reduction in seizure frequency was 14.9% with placebo and 29.3% with low exposure everolimus and 39.6% with high exposure everolimus. Adverse events leading to treatment discontinuation occurred in 2% of placebo-treated patients, 5% of low exposure everolimus patients and 3% of high exposure everolimus patients.

META-ANALYSES

A meta-analysis examined the complete response rate to first-line therapy in patients with metastatic RCC utilizing the antiangiogenic agents (bevacizumab, sunitinib [Sutent], pazopanib [Votrient], or sorafenib [Nexavar]) versus the complete response rates with interferon or placebo (control arm) in this same setting.¹⁸⁴ A total of 2,747 patients across 5 randomized, controlled trials (4 phase 3 trials and 1 phase 2 trial) were analyzed. The complete response rate was 2% (95% CI, 1.2 to 2.8) in the group treated with antiangiogenesis agents compared to 1.4% (95% CI, 0.7 to 2.1) in the control arm. Removing bevacizumab from the study group, the overall complete response rate to the tyrosine kinase inhibitors (sunitinib, pazopanib, and sorafenib) was 1.6% (94% CI, 0.1 to 2.5). The authors concluded that, although the antiangiogenic agents have greater efficacy in terms of PFS and overall response rate, they did not increase the curative rate of metastatic disease. A subsequent Bayesian network meta-analysis through April 2019 evaluated 25 randomized clinical trials (n=13,010) to assess the efficacy and safety of first-line regimens for the treatment of RCC.¹⁸⁵ The authors found that overall survival was most improved with pembrolizumab plus axitinib (HR, 0.53; 95% credible interval [CrI], 0.38 to 0.73) compared to sunitinib. Compared to sunitinib and regarding agents included in this review, cabozantinib (HR, 0.66; 95% CrI, 0.46 to 0.94), pembrolizumab plus axitinib (HR, 0.69; 95% CrI, 0.57 to 0.84), and avelumab plus axitinib (HR, 0.69; 95% CrI, 0.56 to 0.85) were statistically superior.

A systematic review and network meta-analysis examined the effectiveness of first-line treatments for advanced RCC.¹⁸⁶ There were 11 randomized, controlled trials included in the meta-analysis. Regarding PFS, first-line sunitinib (Sutent) was superior to bevacizumab plus interferon-alfa (HR, 0.79; 95% CI, 0.64 to 0.96), everolimus (Afinitor) (HR, 0.7; 95% CI, 0.56 to 0.87), sorafenib (Nexavar) (HR, 0.56; 95% CI, 0.4 to 0.77), and temsirolimus plus bevacizumab (HR, 0.74; 95% CI, 0.56 to 0.96). There was no significant difference in PFS between first-line sunitinib and axitinib (Inlyta), pazopanib (Votrient), or tivozanib.

A systematic review compared the safety and efficacy of axitinib (Inlyta), sorafenib (Nexavar), pazopanib (Votrient), and everolimus (Afinitor) in the second-line setting of patients with metastatic RCC.¹⁸⁷ At the time of the review, sunitinib (Sutent) was established as the most often utilized first-line agent and this review attempted to define the optimal second-line therapy in the absence of head-to-head trials other than the trial showing a statistically significant improvement in PFS of axitinib versus sorafenib in the second-line setting. Four randomized, controlled trials met the inclusion criteria and were analyzed using Bayesian mixed treatment comparison models to assess relative effectiveness on multiple endpoints including objective response rate, dose limiting grade 3 to 4 toxicities, treatment discontinuations, and PFS. The reported results concluded that all 4 agents provided a clinically meaningful PFS benefit, but axitinib was superior to pazopanib (HR, 0.64; 95% CI, 0.42 to 0.96) and sorafenib (HR, 0.7; 95% CI, 0.57 to 0.87) in terms of PFS. In patients who had received a prior TKI, the PFS was similar between axitinib and everolimus. The indirect statistical analysis revealed that the risk of treatment discontinuation was highest with everolimus and pazopanib. Fatigue was a predominant toxicity with axitinib and everolimus, while hand-foot syndrome occurred with axitinib and sorafenib but was highest with sorafenib. There was an elevated risk of grade 3 to 4 stomatitis with everolimus

and, although pazopanib had the lowest risk of fatigue, hand-foot syndrome, rash, and stomatitis, it did have the highest rate of drug discontinuation, primarily due to elevated LFTs.

A meta-analysis compared VEGFR-TKIs versus mTOR inhibitors in the setting of non-clear cell RCC.¹⁸⁸ A total of 4 randomized controlled trials were included for evaluation. The analysis suggests that TKIs significantly reduced the risk of disease progression compared with mTOR inhibitors (HR, 0.71; 95% CI, 0.6 to 0.84; $p < 0.0001$); however, no significant difference was found between TKIs and mTOR inhibitors with regard to overall survival (HR, 0.86; 95% CI, 0.67 to 1.12; $p=0.27$). These results confirm that current the standard of treatment for clear cell RCC apply to non-clear cell RCC.

A meta-analysis indirectly compared PFS and overall survival of first-line and second-line therapies in metastatic RCC.¹⁸⁹ There were 26 randomized controlled trials with a combined 13,893 patients. Cabozantinib, used as first-line, demonstrated the highest improved PFS (HR, 0.26; 95% CrI, 0.14 to 0.44) followed by avelumab plus axitinib and pembrolizumab plus axitinib (HR, 0.27; surface under the cumulative ranking curve [SUCRA], 90%). SUCRA was used to estimate the probability of being the best treatment. When evaluating overall survival, pembrolizumab plus axitinib had the highest likelihood of being a preferred treatment (HR, 0.41; 95% CrI, 0.16 to 0.85). The lowest discontinuation due to adverse events occurred in the avelumab plus axitinib group compared with placebo plus interferon (HR, 1.04; 95% CrI, 0.54 to 1.86). Cabozantinib was the most effective treatment for second-line therapy with regard to PFS (HR, 0.17; 95% CrI 0.12 to 0.24), followed by pazopanib (HR, 0.56; 95% CrI, 0.28 to 1; SUCRA, 76%).

SUMMARY

In the past decade, a clearer understanding of the pathogenesis and signaling pathways associated with renal cell carcinoma (RCC) has led to a host of newly approved agents for the treatment of advanced, surgically unresectable RCC. Targeted therapies utilizing tyrosine kinase inhibitors (TKIs), and immune checkpoint inhibitors (CPI), either alone or in combination, have become the usual first-line and second-line treatment options for advanced RCC due to their improved efficacy and tolerability compared to the historical use of cytokines, such as interferon and interleukin-2. Most recently in January 2021, the Food and Drug Administration (FDA) approved the use of cabozantinib (Cabometyx), in combination with nivolumab (Opdivo), for the first-line treatment of advanced renal cell carcinoma.

TKI plus CPI combinations including either axitinib or lenvatinib plus pembrolizumab or cabozantinib plus nivolumab are all category 1, preferred first-line treatment options for patients with relapsed or stage 4 RCC with clear cell histology and favorable risk according to the National Comprehensive Cancer Network (NCCN) guidelines. Axitinib plus avelumab as well as single agents pazopanib and sunitinib are category 2A other recommended regimens for this same group of patients while single agent cabozantinib is a NCCN category 2B recommendation in this scenario. The same TKI/CPI combinations are also category 1, preferred options for patients with poor/intermediate risk rather than favorable risk. Single agent cabozantinib is a category 2A preferred option in the first-line setting of these poor/intermediate risk patients, while pazopanib or sunitinib and combination therapy with axitinib plus avelumab are category 2A, other recommended regimen recommendations for poor/intermediate risk patients in the first-line setting. The NCCN guidelines no longer recommend sorafenib (Nexavar) as a first-line option.

For subsequent therapy in patients with relapsed or stage 4 surgically unresectable RCC with a predominantly clear cell histology, single agent cabozantinib is a NCCN category 1, preferred

recommendation. This NCCN category 1, preferred recommendation is based on head-to-head trials conducted with cabozantinib and everolimus (Afinitor). In this setting of subsequent therapy, both axitinib monotherapy and combination therapy with lenvatinib plus everolimus are also category 1 recommendations. Monotherapy with sunitinib, pazopanib, or tivozanib (Fotivda) as well as the combinations of axitinib or lenvatinib with pembrolizumab and cabozantinib with nivolumab are category 2A recommendations. The NCCN has changed sorafenib to a 3 recommendation for subsequent therapy.

In November 2017, sunitinib became the first FDA-approved TKI for the adjuvant treatment of RCC patients with a high risk of disease recurrence. Sunitinib, given for nine 6-week cycles, in the adjuvant setting is indicated for use in patients with locoregional disease after undergoing nephrectomy to lessen the risk of disease recurrence. Despite the FDA approval, NCCN guidelines have removed the recommendation for use of adjuvant sunitinib (Sutent) in patients with stage 2 disease from the guidelines and give the use of adjuvant sunitinib (Sutent) in patients with stage 3 disease an NCCN category 3 recommendation, indicating disagreement amongst the NCCN panelists that the intervention is appropriate.

Everolimus (Afinitor), pazopanib (Votrient), sorafenib (Nexavar), lenvatinib (Lenvima), and sunitinib (Sutent) all have other FDA-approved indications in addition to RCC. These agents are considered second-line therapies in these disease states or are used in clinical situations where surgery or local therapy is not an option.

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