

Disease Management Project

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Physician's Guide to

Renal Cell Carcinoma

Namita Chittoria, MD, and Brian I. Rini, MD

In collaboration with



BulletinHealthcare



Disease Management Project

Dear Healthcare Professional,

Welcome to the latest edition of the *Cleveland Clinic Physician's Guide to Renal Cell Carcinoma* (RCC). It comes to you courtesy of the Cleveland Clinic's Disease Management Project (DMP) in collaboration with Bulletin Healthcare, the leading provider of medical news updates.

We asked leading experts Namita Chittoria, MD, and Brian I. Rini, MD, to develop this guide to this prevalent disease. We hope you find it valuable in your efforts to provide positive patient outcomes.

The *Cleveland Clinic Physician's Guide to Renal Cell Carcinoma* was developed to keep you well versed on everything from diagnosis through treatment and anticipated outcomes. In addition, you'll receive news updates on RCC from Bulletin Healthcare, which also prepares briefings for such medical associations as the American Society of Clinical Oncology (ASCO) and the American Medical Association (AMA).

We trust you will find the guide and news updates useful and educational. Please forward your thoughts about them to me at diseasemanagement@ccf.org.

My sincere thanks,

William Carey, MD

Editor-in-Chief Disease Management Project Cleveland Clinic



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Introduction

Definition

Renal cell carcinoma (RCC) accounts for 90% to 95% of malignant neoplasms arising from the kidney. Recent advances in surgical and systemic therapies have significantly changed the management of RCC. Targeted therapies against the vascular endothelial growth factor (VEGF) pathway have extended the lives of the patients with advanced disease significantly, with median overall survival currently exceeding 2 years.¹

Epidemiology

RCC accounts for 2% to 3% of all malignant diseases in adults. It is the seventh most common cancer in men and the ninth most common in women. In the United States, there are approximately 65,000 new cases each year and about 13,500 deaths from RCC annually.² The incidence of RCC in the US has increased over time.³⁻⁵ Between 1992 and 2005, the incidence rose by 1.8% and 2.1% among white men and white women, respectively, and by 2.1% and 1.7% among black men and black women, respectively. In an analysis of more than 29,000 cases from the Surveillance, Epidemiology, and End Results (SEER) database, this increased incidence has been associated with a steady decrease in the average size of tumors at presentation (6.7 cm vs 5.9 cm in 1988 and 2002, respectively).³ Despite the earlier detection of smaller kidney tumors, the rate of RCC-related mortality has increased,^{6,7} suggesting that recurrence and advanced disease are responsible for mortality.

Within the US, Asian Americans and Pacific Islanders have the lowest incidence of renal cancers compared with American Indians/Alaskan natives, Hispanics, Caucasians, and African Americans.² Globally, the incidence of RCC varies widely from region to region, with the highest rates observed in the Czech Republic and in North America.⁸

RCC is approximately 50% more common in men than in women.⁹ It usually occurs between the sixth and eighth decades of life, with a median age of 65.

Risk Factors

Inhaled tobacco smoke is clearly implicated in the etiology of RCC, with a strong dose-dependent increase in risk associated with numbers of cigarettes smoked per day and a substantial reduction in risk for long-term former smokers.¹⁰ Higher body mass index (BMI) and elevated blood pressure independently increase the long-term risk of renal cell cancer in men. A reduction in blood pressure has been associated with a reduced risk of RCC.¹¹ These 3 risk factors together are associated with 49% of cases.¹²

Other modifiable risk factors, although not convincingly associated, include exposure to asbestos, trichloroethylene, or thiazide, and use of acetaminophen or other analgesic drugs. Renal cell carcinoma also seems to be more common in patients with chronic hepatitis C infection,¹³ end-stage renal failure, acquired renal cystic disease,¹⁴ and tuberous sclerosis¹⁵ than in the general population (Table 1).

Table 1. Renal CellCarcinoma Risk Factors

Tobacco smoking
Obesity
Hypertension
Occupational exposures
Polycystic kidney disease
Chronic Hepatitis C infection
Genetic

Detection & Diagnosis

Genetics

Individuals with a family history of RCC have a 2.8-fold greater chance for developing renal cancer during their lifetimes¹⁶ and account for about 4% of all RCC cases. Studies of families with inherited RCC have enabled the identification of 6 hereditary RCC syndromes: von Hippel-Lindau (VHL), hereditary papillary renal carcinoma (HPRC), Birt-Hogg-Dubé syndrome (BHD), hereditary leiomyomatosis RCC (HLRCC), succinate dehydrogenase (SDH)-associated familial cancer, and tuberous sclerosis complex (TSC) (Table 2). The predisposing genes associated with these syndromes are VHL, MET, FLCN, FH, SDH, TSC1 and TSC2, respectively.¹⁷

Pathophysiology

RCC consists of a heterogeneous group of tumors with distinct genetic and metabolic defects, as well as histopathologic and clinical features (Table 3).¹⁷ Medullary carcinomas are rare but aggressive, and are exclusively associated with sickle cell trait.

Signs and Symptoms

Renal cancers have been called "the internist's tumor" and are among the great mimics in medicine because they present with systemic symptoms unrelated to the kidney cancer, such as hypertension (renin), hypercalcemia (PTHrP), polycythemia (erythropoietin), eosinophilia, leukemoid reactions, Cushing's syndrome (ACTH), fever or wasting syndromes, and Stauffer's syndrome (reversible hepatic dysfunction after primary tumor removal). Most cases of RCC are diagnosed incidentally on radiographic investigation done for other reasons. The classic triad of hematuria, abdominal pain, and a palpable mass is present in $\leq 10\%$ of cases.

Signs or symptoms resulting from metastatic disease include bone pain, adenopathy, pulmonary symptoms attributable to lung parenchyma or mediastinal metastases, upper GI bleed, and neurologic deficits.

Diagnosis

The initial workup consists of taking a detailed medical history and performing a physical examination. Appropriate laboratory investigations include a complete blood cell count, a comprehensive metabolic panel (including evaluation of serum calcium level, liver function, and lactate dehydrogenase and serum creatinine levels), a coagulation profile, and urinalysis. Imaging studies should include computed tomography (CT) scans of the abdomen and pelvis (with and without contrast) (Figure 1) and chest imaging (either chest radiograph or CT scan).



Figure 1. CT Scan of a Patient with Renal Cell Carcinoma Before (A) and After (B) Intravenous Contrast.

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Syndrome	Gene (Chromosome)	Histology	Major clinical manifestations
von Hippel-Lindau	VHL tumor suppressor gene (3p25-26)	Clear cell	Autosomal dominant, retinal angioma, CNS hemangioblastomas, pheochromocytomas, pancreatic islet cell tumors, paragangliomas, cystadenoma of broad ligament or epididymis.
Hereditary papillary renal carcinoma	MET proto-oncogene (7q31)	Type 1 papillary	Autosomal-dominant, multifocal, bilateral renal cell tumors.
Birt-Hogg-Dubé syndrome	FLCN tumor suppressor gene (17p11.2)	Chromophobe, hybrid oncocytoma	Autosomal-dominant, cutaneous fibro-folliculoma, pulmonary cysts and spontaneous pneumothorax.
Hereditary leiomyomatosis and renal cell carcinoma	FH tumor suppressor gene (1q42-43)	Type 2 papillary	Autosomal-dominant, leiomyomas of skin and uterus, unilateral, solitary, and aggressive renal cell tumors.
Succinate dehydrogenase (SDH)- associated familial cancer ⁴⁰	SDH-B subunit (1p35-36) SDH-D subunit (11q23)	Clear cell, chromophobe, papillary type 2, renal oncocytoma	Head and neck para-ganglioma, and adrenal or extra- adrenal pheochromocytomas.
Tuberous sclerosis complex	TSC1 (9q34) TSC2 (16p13)	Clear cell (common)	Autosomal-dominant, facial angiofibromas, multifocal renal angiolipomas, neurologic disorders or seizures, lymphangiomyomatosis of the lungs.
Adapted from <i>The Lanc</i> 2009, with permission	cet Vol. 373, Rini BI, Ca from Elsevier.	ampbell SC, Escudier B	, Renal Cell Carcinoma, pages 1119-1132, Copyright

Table 2: Hereditary Renal Cell Carcinoma Syndromes

Table 3: Histologic Classification of Renal Cell Carcinoma

Histology	Frequency	Cell of Origin	Characteristics			
Clear cell	60%-70%	Proximal tubule	Cells with clear cytoplasm with acinar or sarcomatoid growth pattern.			
Papillary	5%-15%	Proximal tubule	Type I: papillae lined with a layer of tumor cells with scant pale cytoplasm and low-grade nuclei.			
			Type II: abundant eosinophilic cytoplasm and large pseudo stratified nuclei with prominent nucleoli; aggressive subtype.			
Chromophobic	5%-10%	Cortical collecting duct	Cells are large with finely reticulated eosinophilic cytoplasm, and atypical nuclei with perinuclear halo with solid, tubular or sarcomatoid growth pattern; indolent course.			
Oncocytic	5%-10%	Cortical collecting duct	Benign neoplasms.			
Collecting duct	<1%	Medullary collecting duct	Papillary or sarcomatoid growth pattern.			
Adapted from <i>The Lancet</i> Vol. 373, Rini BI, Campbell SC, Escudier B, Renal Cell Carcinoma, pages 1119-1132, Copyright 2009 with permission from Elsevier.						

Abdominal magnetic resonance imaging (MRI) is used to evaluate tumor extension into the inferior vena cava. MRI can be used instead of CT when contrast media cannot be administered due to allergy or renal insufficiency.^{18,19} A bone scan or brain imaging is not routinely performed unless signs or symptoms suggest involvement of these areas. PET is not used to diagnose or follow up kidney cancer in any circumstance.²⁰ Needle biopsy is not routinely used to establish diagnosis in patients with large renal masses and radiologic characteristics of malignancy. These patients often undergo immediate kidney removal, which is both diagnostic and therapeutic. However, needle biopsy may be valuable in patients with small (< 3 cm) renal masses not requiring nephrectomy.²¹

A differential diagnosis of urothelial carcinoma should be considered in a patient with a central renal mass and urine cytology. Alternatively, ureteroscopy should be pursued in addition to biopsy, as indicated.

The severity of disease is staged on the basis of imaging studies and the American Joint Committee on Cancer (AJCC) Cancer Staging Manual (Table 4). Approximately 50% of RCC patients present with localized disease, 25% with locally advanced disease, and 25% to 30% with metastatic disease.

Primary Tumor (T)						
Тх	Primary tumor can not be assessed					
ТО	No evidence of primary tumor					
T1a	Tumor \leq 4 cm, confined to the	e kidney				
T1b	Tumor 4 cm to < 7 cm, confir	ned to the kidney				
T2a	Tumor \geq 7 cm to < 10 cm, c	onfined to the kidney				
T2b	Tumor \geq 10 cm, confined to t	he kidney				
ТЗа	Tumor extends into the renal v perinephric fat but not beyond	ein or its segmental branches or Gerota's fascia	invades adrenal gland or			
T3b	Tumor extends into the vena c	ava below diaphragm				
T3c	Tumor extends into the vena c	ava above the diaphragm or inva	ades the wall of vena cava			
Τ4	Tumor invades beyond Gerota'	s fascia				
Regional Lymph Nodes (N)						
N1	Metastasis in 1 regional lymph	n node				
N2	Metastasis in > 1 regional lym	nph node				
Distant Metastases (M)						
M1	Distant metastasis present					
Anatomic Stage						
Stage I	T1	NO	MO			
Stage II	T2	NO	MO			
Stage III	T1/ T2	N1	MO			
	Т3	NO/ N1	MO			
Stage IV	T4 Any N MO					
	Any T	Any N	M1			
Reprinted with permission from et al., eds. AJCC Cancer Stag	n Springer (American Joint Comi ging Manual. 7th ed. New York,	nittee on Cancer. Kidney. In: Eda NY: Springer; 2010479-89).	ge SB, Byrd DR, Compton CC,			

Table 4. American Joint Committee on Cancer TNM Staging System for Kidney Cancer



Prognostic Criteria

The Memorial Sloan-Kettering Cancer Center prognostic criteria are commonly used in patients with metastatic disease. These criteria correlate the following features with poor outcomes in patients treated with either cytokines or chemotherapy agents in various clinical trials before the era of targeted therapy:

- a. Poor performance status (Karnofsky performance status < 80%)
- b. Elevated LDH (> $1.5 \times$ upper limit of normal)
- c. Elevated corrected calcium (> 10 mg/dL)
- d. Low hemoglobin (below lower limit of normal)
- e. Time from initial RCC diagnosis to the start of interferon-alpha therapy of < 1 year.

These risk factors categorize patients' prognoses into favorable (0 risk factors), intermediate (1-2 risk factors), and poor (3-5 risk factors) risk groups, which were associated with a median survival of 30, 14, and 5 months, respectively.²²

Cleveland Clinic has developed another prognostic model for patients with metastatic clear-cell RCC treated with vascular endothelial growth factor (VEGF)-targeted therapy. This single-institution, retrospective study found the following to be predictors of poor outcome:

- a. An interval from diagnosis to treatment < 2 years
- b. Baseline corrected serum calcium < 8.5 mg/dL or > 10 mg/dL
- c. Eastern Cooperative Oncology Group performance status > 0
- d. Neutrophil count > 4.5×10^{9} /L
- e. Platelet count > 300×10^{9} /L

The median progression-free survival (PFS) in patients with 0 or 1 adverse prognostic factors was 20.1 months compared with 13 months in patients with 2 adverse prognostic factors and 3.9 months in those with 3 or more adverse prognostic factors.²³

In another study, the outcomes data from the phase III trial in which sunitinib was compared with interferon-alpha were used to derive a prognostic model for those treated with sunitinib alone (n = 375). A prognostic nomogram was created by using 11 factors, including corrected serum calcium, number of metastatic sites, hemoglobin, prior nephrectomy, presence of lung metastases, presence of liver metastases, Eastern Cooperative Oncology Group (ECOG) performance status, thrombocytosis, time from diagnosis to treatment, alkaline phosphatase, and LDH.²⁴

Although various prognostic models exist, robust clinical and biologic features predictive of outcome in patients with metastatic RCC are scarce. Until appropriate predictive patient variables are identified, available effective agents should be offered even to patients with poor prognoses. Targeted therapies against the VEGF pathway have significantly extended the lives of patients with advanced disease. The median overall survival (OS) duration now exceeds 2 years.¹ Overall, the estimated average 5-year survival rates for patients with RCC are 96% for those presenting with stage I disease, 82% for those with stage II, 64% for stage III, and 23% for stage IV.

After failure of first-line VEGFR-TKIs sunitinib or sorafenib in aRCC,

CHANGE THEIR COURSE

AFINITOR[®] (everolimus) Tablets is the first and only oral mTOR inhibitor indicated for the treatment of adult patients

ral mTOR inhibitor indicated for the treatment of adult patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib

Abbreviations: aRCC, advanced renal cell carcinoma; BSC, best supportive care; mTOR, mammalian target of rapamycin; PFS, progression-free survival; VEGFR-TKI, vascular endothelial growth factor receptor-tyrosine kinase inhibitor.

Proven experience¹

- AFINITOR is now approved in 5 indications, with experience in aRCC
- A safety profile based on data in 274 patients with aRCC

3x antitumor effect¹⁻³

 AFINITOR inhibits angiogenesis, growth and proliferation, and metabolism in in vitro and/or in vivo studies

More than 2x median PFS^{1,4*}

 AFINITOR (n=277): 4.9 months (95% Cl, 4.0-5.5); placebo (n=139): 1.9 months (95% Cl, 1.8-1.9) (HR=0.33; 95% Cl, 0.25-0.43; log-rank *P*<0.0001)

*In the RECORD-1 trial, AFINITOR + BSC (n=277) extended PFS vs placebo + BSC (n=139) after progression on sunitinib or sorafenib (4.9 months [95% CI, 4.0-5.5] vs 1.9 months [95% CI, 1.8-1.9]; log-rank P<0.0001).^{1,4}

Important Safety Information

AFINITOR is contraindicated in patients with hypersensitivity to everolimus, to other rapamycin derivatives, or to any of the excipients.

Noninfectious Pneumonitis:

- Noninfectious pneumonitis was reported in up to 19% of patients treated with AFINITOR. The incidence of Common Terminology Criteria (CTC) grade 3 and 4 noninfectious pneumonitis was up to 4.0% and up to 0.2%, respectively. Fatal outcomes have been observed
- Monitor for clinical symptoms or radiological changes
- Opportunistic infections such as pneumocystis jiroveci pneumonia (PJP) should be considered in the differential diagnosis
- Manage noninfectious pneumonitis by dose reduction or discontinuation until symptoms resolve, and consider the use of corticosteroids
- For patients who require use of corticosteroids, prophylaxis for PJP may be considered
- The development of pneumonitis has been reported even at a reduced dose

Infections:

- AFINITOR has immunosuppressive properties and may predispose patients to bacterial, fungal, viral, or protozoal infections (including those with opportunistic pathogens)
- Localized and systemic infections, including pneumonia, mycobacterial infections, other bacterial infections; invasive fungal infections such as aspergillosis, candidiasis, or PJP; and viral infections, including reactivation of hepatitis B virus, have occurred
- Some of these infections have been severe (eg, leading to sepsis, respiratory failure, or hepatic failure) or fatal
- Physicians and patients should be aware of the increased risk of infection with AFINITOR
- Treatment of preexisting invasive fungal infections should be completed prior to starting treatment with AFINITOR
- Be vigilant for signs and symptoms of infection and institute appropriate treatment promptly; interruption or discontinuation of AFINITOR should be considered
- Discontinue AFINITOR if invasive systemic fungal infection is diagnosed and institute appropriate antifungal treatment
- PJP has been reported in patients who received everolimus, sometimes with a fatal outcome. This may be associated with concomitant use of corticosteroids or other immunosuppressive agents; consider prophylaxis for PJP when concomitant use of these agents is required

Continued on next page

Important Safety Information (cont)

Oral Ulceration:

- Mouth ulcers, stomatitis, and oral mucositis have occurred in patients treated with AFINITOR at an incidence ranging from 44% to 78% across the clinical trial experience. Grade 3/4 stomatitis was reported in 4% to 9% of patients
- In such cases, topical treatments are recommended, but alcohol-, hydrogen peroxide-, iodine-, or thyme-containing mouthwashes should be avoided
- Antifungal agents should not be used unless fungal infection has been diagnosed

Renal Failure:

• Cases of renal failure (including acute renal failure), some with a fatal outcome, have been observed in patients treated with AFINITOR

Impaired Wound Healing:

- Everolimus delays wound healing and increases the occurrence of wound-related complications like wound dehiscence, wound infection, incisional hernia, lymphocele, and seroma
- These wound-related complications may require surgical intervention. Exercise caution with the use of AFINITOR in the perisurgical period

Laboratory Tests and Monitoring:

- Elevations of serum creatinine and proteinuria have been reported. Renal function (including measurement of blood urea nitrogen, urinary protein, or serum creatinine) should be evaluated prior to treatment and periodically thereafter, particularly in patients who have additional risk factors that may further impair renal function
- Hyperglycemia, hyperlipidemia, and hypertriglyceridemia have been reported. Blood glucose and lipids should be evaluated prior to treatment and periodically thereafter. More frequent monitoring is recommended when AFINITOR is coadministered with other drugs that may induce hyperglycemia. Management with appropriate medical therapy is recommended. When possible, optimal glucose and lipid control should be achieved before starting a patient on AFINITOR
- Reductions in hemoglobin, lymphocytes, neutrophils, and platelets have been reported. Monitoring of complete blood count is recommended prior to treatment and periodically thereafter

Drug-Drug Interactions:

- Avoid coadministration with strong CYP3A4/PgP inhibitors (eg, ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, voriconazole)
- Use caution and reduce the AFINITOR dose to 2.5 mg daily if coadministration with a moderate CYP3A4/PgP inhibitor is required (eg, amprenavir, fosamprenavir, aprepitant, erythromycin, fluconazole, verapamil, diltiazem)
- Avoid coadministration with strong CYP3A4/PgP inducers (eg, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital); however, if coadministration is required, consider doubling the daily dose of AFINITOR using increments of 5 mg or less

Hepatic Impairment:

- Exposure to everolimus was increased in patients with hepatic impairment
- For patients with severe hepatic impairment (Child-Pugh class C), AFINITOR may be used at a reduced dose if the desired benefit outweighs the risk. For patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment, a dose reduction is recommended

Vaccinations:

• The use of live vaccines and close contact with those who have received live vaccines should be avoided during treatment with AFINITOR

Embryo-Fetal Toxicity:

- Fetal harm can occur if AFINITOR is administered to a pregnant woman
- Advise female patients of reproductive potential to use highly effective contraception while using AFINITOR and for up to 8 weeks after ending treatment

Adverse Reactions:

- The most common adverse reactions (incidence ≥30%) were stomatitis (44%), infections (37%), asthenia (33%), fatigue (31%), cough (30%), and diarrhea (30%)
- The most common grade 3/4 adverse reactions (incidence ≥5%) were infections (10%), dyspnea (7%), stomatitis (5%), and fatigue (5%)

Laboratory Abnormalities:

- The most common laboratory abnormalities (incidence ≥50%, all grades) were: decreased hemoglobin (92%) and lymphocytes (51%); and increased cholesterol (77%), triglycerides (73%), glucose (57%), and creatinine (50%)
- The most common grade 3/4 laboratory abnormalities (incidence ≥5%) were decreased hemoglobin (13%), lymphocytes (18%), and phosphate (6%), and increased glucose (16%)

Please see Brief Summary of Prescribing Information on adjacent pages.

References: 1. AFINITOR [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2014. **2.** Yuan R, Kay A, Berg W, Lebwohl D. Targeting tumorigenesis: development and use of mTOR inhibitors in cancer therapy. *J Hematol Oncol.* 2009;2:45. **3.** Dancey JE. Inhibitors of the mammalian target of rapamycin. *Expert Opin Investig Drugs.* 2005;14:313-328. **4.** Motzer RJ, Escudier B, Oudard S, et al. Phase 3 trial of everolimus for metastatic renal cell carcinoma: final results and analysis of prognostic factors. *Cancer.* 2010;116(18):4256-4265.



AFINITOR[®] (everolimus) tablets for oral administration AFINITOR[®] DISPERZ (everolimus tablets for oral suspension) Initial U.S. Approval: 2009

BRIEF SUMMARY: Please see package insert for full prescribing information. 1 INDICATIONS AND USAGE

AFINITOR[®] is indicated for the treatment of adult patients with advanced renal cell carcinoma (RCC) after failure of treatment with sunitinib or sorafenib.

4 CONTRAINDICATIONS

AFINITOR is contraindicated in patients with hypersensitivity to the active substance, to other rapamycin derivatives, or to any of the excipients. Hypersensitivity reactions manifested by symptoms including, but not limited to, anaphylaxis, dyspnea, flushing, chest pain, or angioedema (e.g., swelling of the airways or tongue, with or without respiratory impairment) have been observed with everolimus and other rapamycin derivatives.

5 WARNINGS AND PRECAUTIONS

5.1 Non-infectious Pneumonitis

Non-infectious pneumonitis is a class effect of rapamycin derivatives, including AFINITOR. Non-infectious pneumonitis was reported in up to 19% of patients treated with AFINITOR in clinical trials. The incidence of Common Terminology Criteria (CTC) Grade 3 and 4 non-infectious pneumonitis was up to 4.0% and up to 0.2%, respectively [see Adverse Reactions (6.1, 6.2, 6.3, 6.4, 6.5) in the full prescribing information]. Fatal outcomes have been observed.

Consider a diagnosis of non-infectious pneumonitis in patients presenting with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough, or dyspnea, and in whom infectious, neoplastic, and other causes have been excluded by means of appropriate investigations. Opportunistic infections such as pneumocystis jiroveci pneumonia (PJP) should be considered in the differential diagnosis. Advise patients to report promptly any new or worsening respiratory symptoms.

Patients who develop radiological changes suggestive of non-infectious pneumonitis and have few or no symptoms may continue AFINITOR therapy without dose alteration. Imaging appears to overestimate the incidence of clinical pneumonitis.

If symptoms are moderate, consider interrupting therapy until symptoms improve. The use of corticosteroids may be indicated. AFINITOR may be reintroduced at a daily dose approximately 50% lower than the dose previously administered [see Table 1 in Dosage and Administration (2.2) in the full prescribing information].

For cases of Grade 3 non-infectious pneumonitis interrupt AFINITOR until resolution to less than or equal to Grade 1. AFINITOR may be re-introduced at a daily dose approximately 50% lower than the dose previously administered depending on the individual clinical circumstances [see Dosage and Administration (2.2) in the full prescribing information]. If toxicity recurs at Grade 3, consider discontinuation of AFINITOR. For cases of Grade 4 non-infectious pneumonitis, discontinue AFINITOR. Corticosteroids may be indicated until clinical symptoms resolve. For patients who require use of corticosteroids for treatment of non-infectious pneumonitis, prophylaxis for PJP may be considered. The development of pneumonitis has been reported even at a reduced dose.

5.2 Infections

AFINITOR has immunosuppressive properties and may predispose patients to bacterial, fungal, viral, or protozoal infections, including infections with opportunistic pathogens [see Adverse Reactions (6.1, 6.2, 6.3, 6.4, 6.5) in the full prescribing information]. Localized and systemic infections, including pneumonia, mycobacterial infections, other bacterial infections, invasive fungal infections, such as aspergillosis, candidiasis, or pneumocystis jiroveci pneumonia (PJP) and viral infections including reactivation of hepatitis B virus have occurred in patients taking AFINITOR. Some of these infections have been severe (e.g., leading to sepsis, respiratory or hepatic failure) or fatal. Physicians and patients should be aware of the increased risk of infection with AFINITOR. Complete treatment of pre-existing invasive fungal infections prior to starting treatment with AFINITOR. While taking AFINITOR, be vigilant for signs and symptoms of infection; if a diagnosis of an infection is made, institute appropriate treatment promptly and consider interruption or discontinuation of AFINITOR. If a diagnosis of invasive systemic fungal infection is made, discontinue AFINITOR and treat with appropriate antifungal therapy.

Pneumocystis jiroveci pneumonia, some with a fatal outcome, has been reported in patients who received everolimus. This may be associated with concomitant use of corticosteroids or other immunosuppressive agents. Prophylaxis for PJP should be considered when concomitant use of corticosteroids or other immunosuppressive agents are required.

5.3 Oral Ulceration

Mouth ulcers, stomatitis, and oral mucositis have occurred in patients treated with AFINITOR at an incidence ranging from 44%-78% across the clinical trial experience. Grade 3 or 4 stomatitis was reported in 4%-9% of

patients [see Adverse Reactions (6.1, 6.2, 6.3, 6.4, 6.5) in the full prescribing information]. In such cases, topical treatments are recommended, but alcohol-, hydrogen peroxide-, iodine-, or thyme- containing mouthwashes should be avoided as they may exacerbate the condition. Antifungal agents should not be used unless fungal infection has been diagnosed [see Drug Interactions (7.1)].

5.4 Renal Failure

Cases of renal failure (including acute renal failure), some with a fatal outcome, have been observed in patients treated with AFINITOR [see Laboratory Tests and Monitoring (5.7)].

5.5 Impaired Wound Healing

Everolimus delays wound healing and increases the occurrence of woundrelated complications like wound dehiscence, wound infection, incisional hernia, lymphocele, and seroma. These wound-related complications may require surgical intervention. Exercise caution with the use of AFINITOR in the peri-surgical period.

5.7 Laboratory Tests and Monitoring

Renal Function

Elevations of serum creatinine and proteinuria have been reported in patients taking AFINITOR [see Adverse Reactions (6.1, 6.2, 6.3, 6.4, 6.5) in the full prescribing information]. Monitoring of renal function, including measurement of blood urea nitrogen (BUN), urinary protein, or serum creatinine, is recommended prior to the start of AFINITOR therapy and periodically thereafter. Renal function of patients should be monitored particularly where patients have additional risk factors that may further impair renal function.

Blood Glucose and Lipids

Hyperglycemia, hyperlipidemia, and hypertriglyceridemia have been reported in patients taking AFINITOR *[see Adverse Reactions (6.1, 6.2, 6.3, 6.4, 6.5) in the full prescribing information]*. Monitoring of fasting serum glucose and lipid profile is recommended prior to the start of AFINITOR therapy and periodically thereafter as well as management with appropriate medical therapy. More frequent monitoring is recommended when AFINITOR is co-administered with other drugs that may induce hyperglycemia. When possible, optimal glucose and lipid control should be achieved before starting a patient on AFINITOR.

Hematologic Parameters

Decreased hemoglobin, lymphocytes, neutrophils, and platelets have been reported in patients taking AFINITOR [see Adverse Reactions (6.1, 6.2, 6.3, 6.4, 6.5) in the full prescribing information]. Monitoring of complete blood count is recommended prior to the start of AFINITOR therapy and periodically thereafter.

5.8 Drug-drug Interactions

Due to significant increases in exposure of everolimus, co-administration with strong CYP3A4/PgP inhibitors should be avoided [see Dosage and Administration (2.2, 2.5) in the full prescribing information and Drug Interactions (7.1)].

A reduction of the AFINITOR dose is recommended when co-administered with a moderate CYP3A4/PgP inhibitor [see Dosage and Administration (2.2, 2.5) in the full prescribing information and Drug Interactions (7.1)].

An increase in the AFINITOR dose is recommended when co-administered with a strong CYP3A4/PgP inducer [see Dosage and Administration (2.2, 2.5) in the full prescribing information and Drug Interactions (7.2)].

5.9 Hepatic Impairment

Exposure to everolimus was increased in patients with hepatic impairment [see Clinical Pharmacology (12.3) in the full prescribing information].

For advanced HR+ BC, advanced PNET, advanced RCC, and renal angiomyolipoma with TSC patients with severe hepatic impairment (Child-Pugh class C), AFINITOR may be used at a reduced dose if the desired benefit outweighs the risk. For patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment, a dose reduction is recommended [see Dosage and Administration (2.2) and Clinical Pharmacology (12.3) in the full prescribing information].

For patients with SEGA and mild or moderate hepatic impairment, adjust the dose of AFINITOR Tablets or AFINITOR DISPERZ based on therapeutic drug monitoring. For patients with SEGA and severe hepatic impairment, reduce the starting dose of AFINITOR Tablets or AFINITOR DISPERZ by approximately 50% and adjust subsequent doses based on therapeutic drug monitoring [see Dosage and Administration (2.4, 2.5) in the full prescribing information].

5.10 Vaccinations

During AFINITOR treatment, avoid the use of live vaccines and avoid close contact with individuals who have received live vaccines (e.g., intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines).

For pediatric patients with SEGA that do not require immediate treatment, complete the recommended childhood series of live virus vaccinations according to American Council on Immunization Practices (ACIP) guidelines

prior to the start of therapy. An accelerated vaccination schedule may be appropriate.

5.11 Embryo-fetal Toxicity

Based on the mechanism of action, AFINITOR can cause fetal harm. Everolimus caused embryo-fetal toxicities in animals at maternal exposures that were lower than human exposures. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus [see Use in Specific Populations (8.1)].

Advise female patients of reproductive potential to avoid becoming pregnant and to use highly effective contraception while using AFINITOR and for up to 8 weeks after ending treatment [see Use in Specific Populations (8.6)].

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in another section of the label *[see Warnings and Precautions (5)]*:

- Non-infectious pneumonitis [see Warnings and Precautions (5.1)].
- Infections [see Warnings and Precautions (5.2)].
- Oral ulceration [see Warnings and Precautions (5.3)].
- Renal failure [see Warnings and Precautions (5.4)].
- Impaired wound healing [see Warnings and Precautions (5.5)].

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other trials and may not reflect the rates observed in clinical practice.

6.3 Clinical Study Experience in Advanced Renal Cell Carcinoma

The data described below reflect exposure to AFINITOR (n=274) and placebo (n=137) in a randomized, controlled trial in patients with metastatic renal cell carcinoma who received prior treatment with sunitinib and/or sorafenib. The median age of patients was 61 years (range 27-85), 88% were Caucasian, and 78% were male. The median duration of blinded study treatment was 141 days (range 19-451 days) for patients receiving AFINITOR and 60 days (range 21-295 days) for those receiving placebo.

The most common adverse reactions (incidence \geq 30%) were stomatitis, infections, asthenia, fatigue, cough, and diarrhea. The most common Grade 3-4 adverse reactions (incidence \geq 3%) were infections, dyspnea, fatigue, stomatitis, dehydration, pneumonitis, abdominal pain, and asthenia. The most common laboratory abnormalities (incidence \geq 50%) were anemia, hypercholesterolemia, hypertriglyceridemia, hyperglycemia, lymphopenia, and increased creatinine. The most common Grade 3-4 laboratory abnormalities (incidence \geq 3%) were lymphopenia, hyperglycemia, anemia, hypophosphatemia, and hypercholesterolemia. Deaths due to acute respiratory failure (0.7%), infection (0.7%), and acute renal failure (0.4%) were observed on the AFINITOR arm but none on the placebo arm. The rates of treatment-emergent adverse events (irrespective of causality) resulting in permanent discontinuation were 14% and 3% for the AFINITÓR and placebo treatment groups, respectively. The most common adverse reactions (irrespective of causality) leading to treatment discontinuation were pneumonitis and dyspnea. Infections, stomatitis, and pneumonitis were the most common reasons for treatment delay or dose reduction. The most common medical interventions required during AFINITOR treatment were for infections. anemia. and stomatitis.

Table 6 compares the incidence of treatment-emergent adverse reactions reported with an incidence of \geq 10% for patients receiving AFINITOR 10 mg daily versus placebo. Within each MedDRA system organ class, the adverse reactions are presented in order of decreasing frequency.

Table 6: Adverse Reactions Reported in at Least 10% of Patients with RCC and at a Higher Rate in the AFINITOR Arm than in the Placebo Arm

	AFINITOR 10 mg/day N=274			Placebo N=137		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Any adverse reaction	97	52	13	93	23	5
Gastrointestinal	disorders					
Stomatitis ^a	44	4	<1	8	0	0
Diarrhea	30	1	0	7	0	0
Nausea	26	1	0	19	0	0
Vomiting	20	2	0	12	0	0
Infections and infestations ^b	37	7	3	18	1	0

(continued)

Table 6: Adv	erse Reactions	Reported	in at Least	10% of	Patients	with	RCC
and at a	Higher Rate in	the AFINI	TOR Arm th	an in the	e Placebo	Arm	I I

	AFINITOR 10 mg/day N=274			Placebo N=137			
	All	Grado 3	Grade /	All	Grado 3	Grade /	
	%	%	%	%	%	%	
General disorders and administration site conditions							
Asthenia	33	3	<1	23	4	0	
Fatigue Edema	31	5	0	27	3	<1	
peripheral	25	<1	0	8	<1	0	
Pyrexia Mucosal	20	<1	0	9	0	0	
inflammation	19	1	0	1	0	0	
Respiratory, thor	acic and	mediastina	al disorder	s			
Cough	30	<1	0	16	0	0	
Dyspnea	24	6	1	15	3	0	
Epistaxis	18	0	0	0	0	0	
Pneumonitis ^c	14	4	0	0	0	0	
Skin and subcuta	neous tis	sue disord	ers				
Rash	29	1	0	7	0	0	
Pruritus	14	<1	0	7	0	0	
Dry skin	13	<1	0	5	0	0	
Metabolism and	nutrition	disorders					
Anorexia	25	1	0	14	<1	0	
Nervous system (disorders						
Headache	19	<1	<1	9	<1	0	
Dysgeusia	10	0	0	2	0	0	
Musculoskeletal	and conn	ective tiss	ue disorde	rs			
Pain in extremit	y 10	1	0	7	0	0	
Nedian duration of treatment (d) 141 60							

Grading according to CTCAE Version 3.0

^a Stomatitis (including aphthous stomatitis), and mouth and tongue ulceration.
^b Includes all preferred terms within the 'infections and infestations' system organ class, the most common being nasopharyngitis (6%), pneumonia (6%), urinary tract infection (5%), bronchitis (4%), and sinusitis (3%), and also including aspergillosis (<1%), candidiasis (<1%), and sepsis (<1%).

c Includes pneumonitis, intersitial lung disease, lung infiltration, pulmonary alveolar hemorrhage, pulmonary toxicity, and alveolitis.

Other notable adverse reactions occurring more frequently with AFINITOR than with placebo, but with an incidence of < 10% include:

Gastrointestinal disorders: Abdominal pain (9%), dry mouth (8%), hemorrhoids (5%), dysphagia (4%)

General disorders and administration site conditions: Weight decreased (9%), chest pain (5%), chills (4%), impaired wound healing (< 1%)

Respiratory, thoracic and mediastinal disorders: Pleural effusion (7%), pharyngolaryngeal pain (4%), rhinorrhea (3%)

Skin and subcutaneous tissue disorders: Hand-foot syndrome (reported as palmar-plantar erythrodysesthesia syndrome) (5%), nail disorder (5%), erythema (4%), onychoclasis (4%), skin lesion (4%), acneiform dermatitis (3%)

Metabolism and nutrition disorders: Exacerbation of pre-existing diabetes mellitus (2%), new onset of diabetes mellitus (< 1%)

Psychiatric disorders: Insomnia (9%)

Nervous system disorders: Dizziness (7%), paresthesia (5%)

Eye disorders: Eyelid edema (4%), conjunctivitis (2%)

Vascular disorders: Hypertension (4%), deep vein thrombosis (< 1%) Renal and urinary disorders: Renal failure (3%)

Cardiac disorders: Tachycardia (3%), congestive cardiac failure (1%) Musculoskeletal and connective tissue disorders: Jaw pain (3%)

Hematologic disorders: Hemorrhage (3%)

Key laboratory abnormalities are presented in Table 7.

Table 7: Key Laboratory Abnormalities Reported in Patients with RCC at a
Higher Rate in the AFINITOR Arm than the Placebo Arm

Laboratory parameter	AFIN	ITOR 10 m N=274	ıg/day		Placebo N=137	
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
	70	70	70	70	70	70
Hematology ^a						
Hemoglobin	00	10	4	70	F	.4
uecreased	92	12	I	79	Э	<1
Lymphocytes	51	16	0	00	5	٥
Distolate	51	10	2	20	5	0
decreased	23	1	0	2	0	~1
Neutronhils	20	1	0	2	0	
decreased	14	0	<1	4	0	0
Clinical abamiet		0			0	0
Cholesterol	iy					
increased	77	Δ	0	35	0	0
Trialvcerides			0	00	0	0
increased	73	<1	0	34	0	0
Glucose			-	•	-	-
increased	57	15	<1	25	1	0
Creatinine						
increased	50	1	0	34	0	0
Phosphate						
decreased	37	6	0	8	0	0
Aspartate						
transaminase						
(AST)	05			_		
increased	25	<1	<1	1	0	0
Alanine						
transaminase						
(ALT)	01	-1	0	4	0	0
Riliruhin	21	I	U	4	U	U
increased	3	<1	<1	2	0	0
	0	~ 1	~ 1	2	0	0

Grading according to CTCAE Version 3.0

^a Reflects corresponding adverse drug reaction reports of anemia, leukopenia, lymphopenia, neutropenia, and thrombocytopenia (collectively pancytopenia), which occurred at lower frequency.

6.6 Postmarketing Experience

The following adverse reactions have been identified during post approval use of AFINITOR. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate frequency or establish a causal relationship to drug exposure: acute pancreatitis, cholecystitis, cholelithiasis, arterial thrombotic events and reflex sympathetic dystrophy.

7 DRUG INTERACTIONS

Everolimus is a substrate of CYP3A4, and also a substrate and moderate inhibitor of the multidrug efflux pump PgP. *In vitro*, everolimus is a competitive inhibitor of CYP3A4 and a mixed inhibitor of CYP2D6.

7.1 Agents That May Increase Everolimus Blood Concentrations CYP3A4 Inhibitors and Pap Inhibitors

In healthy subjects, compared to AFINITOR treatment alone there were significant increases in everolimus exposure when AFINITOR was coadministered with:

- ketoconazole (a strong CYP3A4 inhibitor and a PgP inhibitor) C_{max} and AUC increased by 3.9- and 15.0-fold, respectively.
- erythromycin (a moderate CYP3A4 inhibitor and a PgP inhibitor) C_{max} and AUC increased by 2.0- and 4.4-fold, respectively.
- verapamil (a moderate CYP3A4 inhibitor and a PgP inhibitor) C_{max} and AUC increased by 2.3- and 3.5-fold, respectively.

Concomitant strong inhibitors of CYP3A4/PgP should not be used [see Dosage and Administration (2.2, 2.5) in the full prescribing information and Warnings and Precautions (5.8)].

Use caution when AFINITOR is used in combination with moderate CYP3A4/PgP inhibitors. If alternative treatment cannot be administered reduce the AFINITOR dose [see Dosage and Administration (2.2, 2.5) in the full prescribing information and Warnings and Precautions (5.8)].

7.2 Agents That May Decrease Everolimus Blood Concentrations CYP3A4/PgP Inducers

In healthy subjects, co-administration of AFINITOR with rifampin, a strong inducer of CYP3A4 and an inducer of PgP, decreased everolimus AUC and C_{max} by 63% and 58% respectively, compared to everolimus treatment alone. Consider a dose increase of AFINITOR when co-administered with strong CYP3A4/PgP inducers if alternative treatment cannot be administered.

St. John's Wort may decrease everolimus exposure unpredictably and should be avoided [see Dosage and Administration (2.2, 2.5) in the full prescribing information].

7.3 Drugs That May Have Their Plasma Concentrations Altered by Everolimus

Studies in healthy subjects indicate that there are no clinically significant pharmacokinetic interactions between AFINITOR and the HMG-CoA reductase inhibitors atorvastatin (a CYP3A4 substrate) and pravastatin (a non-CYP3A4 substrate) and population pharmacokinetic analyses also detected no influence of simvastatin (a CYP3A4 substrate) on the clearance of AFINITOR.

A study in healthy subjects demonstrated that co-administration of an oral dose of midazolam (sensitive CYP3A4 substrate) with everolimus resulted in a 25% increase in midazolam C_{max} and a 30% increase in midazolam $AUC_{(0-inf)}$.

Coadministration of everolimus and exemestane increased exemestane C_{min} by 45% and C_{2h} by 64%. However, the corresponding estradiol levels at steady state (4 weeks) were not different between the 2 treatment arms. No increase in adverse events related to exemestane was observed in patients with hormone receptor-positive, HER2-negative advanced breast cancer receiving the combination.

Coadministration of everolimus and depot octreotide increased octreotide C_{min} by approximately 50%.

8 USE IN SPECIFIC POPULATIONS 8.1 Pregnancy

Pregnancy Category D

Risk Summary

Based on the mechanism of action, AFINITOR can cause fetal harm when administered to a pregnant woman. Everolimus caused embryo-fetal toxicities in animals at maternal exposures that were lower than human exposures. If this drug is used during pregnancy or if the patient becomes pregnant while taking the drug, apprise the patient of the potential hazard to the fetus [see Warnings and Precautions (5.11)].

Animal Data

In animal reproductive studies, oral administration of everolimus to female rats before mating and through organogenesis induced embryo-fetal toxicities, including increased resorption, pre-implantation and post-implantation loss, decreased numbers of live fetuses, malformation (e.g., sternal cleft), and retarded skeletal development. These effects occurred in the absence of maternal toxicities. Embryo-fetal toxicities in rats occurred at doses $\geq 0.1 \text{ mg/kg} (0.6 \text{ mg/m}^2)$ with resulting exposures of approximately 4% of the exposure (AUC_{0-24h}) achieved in patients receiving the 10 mg daily dose of everolimus. In rabbits, embryotoxicity evident as an increase in resorptions occurred at an oral dose of 0.8 mg/kg (9.6 mg/m²), approximately 1.6 times either the 10 mg daily dose or the median dose administered to SEGA patients on a body surface area basis. The effect in rabbits occurred in the presence of maternal toxicities.

In a pre- and post-natal development study in rats, animals were dosed from implantation through lactation. At the dose of 0.1 mg/kg (0.6 mg/m²), there were no adverse effects on delivery and lactation or signs of maternal toxicity; however, there were reductions in body weight (up to 9% reduction from the control) and in survival of offspring (~5% died or missing). There were no drug-related effects on the developmental parameters (morphological development, motor activity, learning, or fertility assessment) in the offspring.

8.3 Nursing Mothers

It is not known whether everolimus is excreted in human milk. Everolimus and/or its metabolites passed into the milk of lactating rats at a concentration 3.5 times higher than in maternal serum. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from everolimus, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.5 Geriatric Use

In the randomized advanced hormone receptor positive, HER2-negative breast cancer study, 40% of AFINITOR-treated patients were \geq 65 years of age, while 15% were 75 years and over. No overall differences in effective-ness were observed between elderly and younger patients. The incidence of deaths due to any cause within 28 days of the last AFINITOR dose was 6% in patients \geq 65 years of age compared to 2% in patients < 65 years of age. Adverse reactions leading to permanent treatment discontinuation occurred in 33% of patients \geq 65 years of age compared to 17% in patients < 65 years of age [see Warnings and Precautions (5.6) in the full prescribing information].

In two other randomized trials (advanced renal cell carcinoma and advanced neuroendocrine tumors of pancreatic origin), no overall differences in safety or effectiveness were observed between elderly and younger patients. In the randomized advanced RCC study, 41% of AFINITOR treated patients

were ≥ 65 years of age, while 7% were 75 years and over. In the randomized advanced PNET study, 30% of AFINITOR-treated patients were \geq 65 years of age, while 7% were 75 years and over.

Other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out *[see Clinical Pharmacology (12.3) in* the full prescribing information].

No dosage adjustment in initial dosing is required in elderly patients, but close monitoring and appropriate dose adjustments for adverse reactions is recommended [see Dosage and Administration (2.2), Clinical Pharmacology (12.3) in the full prescribing information].

8.6 Females and Males of Reproductive Potential Contraception

Females

AFINITOR can cause fetal harm when administered to a pregnant woman. Advise female patients of reproductive potential to use highly effective contraception while receiving AFINITOR and for up to 8 weeks after ending treatment [see Use in Specific Populations (8.1)].

Infertility Females

Menstrual irregularities, secondary amenorrhea, and increases in luteinizing hormone (LH) and follicle stimulating hormone (FSH) occurred in female patients taking AFINITOR. Based on these clinical findings and findings in animals, female fertility may be compromised by treatment with AFINITOR [see Adverse Reactions (6.2, 6.4, 6.5) and Nonclinical Toxicology (13.1) in the full prescribing information].

Males

AFINITOR treatment may impair fertility in male patients based on animal findings [see Nonclinical Toxicology (13.1) in the full prescribing information].

8.7 Renal Impairment

No clinical studies were conducted with AFINITOR in patients with decreased renal function. Renal impairment is not expected to influence drug exposure and no dosage adjustment of everolimus is recommended in patients with renal impairment [see Clinical Pharmacology (12.3) in the full prescribing information]

8.8 Hepatic Impairment

The safety, tolerability and pharmacokinetics of AFINITOR were evaluated in a 34 subject single oral dose study of everolimus in subjects with impaired hepatic function relative to subjects with normal hepatic function. Exposure was increased in patients with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment [see Clinical Pharmacology (12.3) in the full prescribing information].

For advanced HR+ BC, advanced PNET, advanced RCC, and renal angiomyolipoma with TSC patients with severe hepatic impairment, AFINITOR may be used at a reduced dose if the desired benefit outweighs the risk. For patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment, a dose reduction is recommended [see Dosage and Administration (2.2) in the full prescribing information].

For patients with SEGA who have severe hepatic impairment (Child-Pugh class C), reduce the starting dose of AFINITOR Tablets or AFINITOR DISPERZ by approximately 50%. For patients with SEGA who have mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment, adjustment to the starting dose may not be needed. Subsequent dosing should be based on therapeutic drug monitoring [see Dosage and Administration (2.4, 2.5) in the full prescribing information].

10 OVERDOSAGE

In animal studies, everolimus showed a low acute toxic potential. No lethality or severe toxicity was observed in either mice or rats given single oral doses of 2000 mg/kg (limit test).

Reported experience with overdose in humans is very limited. Single doses of up to 70 mg have been administered. The acute toxicity profile observed with the 70 mg dose was consistent with that for the 10 mg dose.

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Patient Care

Treatment and Outcomes

Stage IA. For tumors \leq 4 cm in diameter, surgical excision by partial nephrectomy (nephron-sparing surgery) (Figure 2) is recommended. The surgical approach can be either open or laparoscopic, depending on surgeon preference, and tumor size and location. The objective of surgery is to spare as many functioning nephrons as possible and to preserve renal function while excising the tumor. Radical nephrectomy is recommended only if the tumor is not amenable to partial nephrectomy.



Figure 2. Partial Nephrectomy Surgical Technique in a Patient with Localized Kidney Cancer. Reprinted with permission from Elsevier (Rini Bl, Campbell SC, Escudier B. Renal cell carcinoma. *Lancet*. 2009;373[9669]:1119-1132). Copyright © 2009 Elsevier. http://www.sciencedirect.com/science/journal/01406736

In patients with decreased life expectancy (or those considered to be at high risk during surgery), options include active surveillance and thermal ablation (cryoablation or radiofrequency ablation). Although distant recurrence-free survival rates are comparable, thermal ablation has been associated with an increased risk of local recurrence compared with conventional surgery.^{25,26}

Stage IB. For 4- to 7-cm tumors, partial nephrectomy, if feasible, or radical nephrectomy is the standard of care.

Stage II and III. Locally advanced tumors are managed with radical nephrectomy, which can require resection of adjacent organs, and with tumor thrombectomy from the renal vein and possibly the inferior vena cava.⁶ Between 40% and 60% of patients can be cured with such an aggressive surgical approach.^{27,28}

After surgical excision, up to 30% of patients with localized tumors experience relapse. The lung is the most common site of distant recurrence, seen in 50% to 60% of patients. The median time to relapse after surgery is approximately 2 years, with most relapses occurring within 5 years. Interferon-alpha and high-dose interleukin-2 (IL-2) have been tested as adjuvant treatments following resection of stage I-II kidney cancer. However, no benefit has been seen in randomized trials.^{29,30} Observation remains standard care after nephrectomy, and eligible patients should be offered enrollment in randomized clinical trials.

The National Comprehensive Cancer Network (NCCN) Kidney Cancer Panel has recommended that patients be seen every 6 months for the first 2 years after surgery and annually thereafter. Each visit should include a history, physical examination, and comprehensive metabolic panel (eg, blood urea nitrogen, serum creatinine, calcium levels, LDH, and liver function tests). Abdominal and chest imaging studies should be done approximately 2 to 6 months after surgery and as clinically indicated thereafter.³¹

Stage IV. Cytoreductive nephrectomy before systemic therapy is recommended in patients with a surgically resectable primary tumor.³² Metastasectomy should be considered in patients with favorable features such as a solitary metastasis or a long interval between initial diagnosis and the development of metastatic disease. In these patients, the 5-year disease-free survival rate can be as high as 30%.

Systemic therapy is recommended for patients with residual metastatic disease, though patients with low-volume indolent metastases may initially undergo a period of observation. Several systemic agents exist today that are non-curative and therefore require long-term sequential therapy with multiple agents and management of toxicity.



Immunotherapy

- a. IL-2. In selected patients with relapsed or medically unresectable stage IV clear-cell RCC, high-dose IL-2 can be considered as a first-line treatment option. Although no demonstrable OS or PFS benefit has been seen, durable complete remissions occur in 7% to 8% of patients. Thus, despite the associated toxicity of capillary leak syndrome, IL-2 remains a viable treatment option reserved for patients with good performance status and acceptable comorbid disorders.⁶ Unfortunately, there are no predictive biomarkers upon which to base the selection of patients for treatment with high-dose IL-2.
- b. **Bevacizumab plus interferon-alpha.** This combination has been associated with a 31% objective response rate with a median PFS of 10.2 months. The regimen is listed as a first-line treatment option for patients with clear-cell RCC with a category 1 designation.

Targeted therapy

Targeted therapy with tyrosine kinase inhibitors has been used widely in first- and second-line treatments. To date, 7 such agents have been approved by the FDA for the treatment of advanced RCC: sunitinib, sorafenib, pazopanib, axitinib, temsirolimus, everolimus, and bevacizumab in combination with interferon.

- a. **VEGF pathway inhibitors:** sunitinib, pazopanib, and bevacizumab plus interferon-alpha are listed as first-line treatment options with a category 1 designation. Sorafenib and axitinib are approved as second-line options.
 - Sunitinib. This multi-kinase inhibitor of VEGF and related receptors has been linked to an advantage in independently assessed objective response rate (39% vs 8%; P < 0.001), median PFS (11 months vs 5 months, P < 0.001), and median OS (26.4 months vs 21.8 months, P = 0.051) vs interferon-alpha in a phase III trial.¹ The trial included untreated patients with metastatic RCC (n = 750) who were given either sunitinib or interferon-alpha. Common toxicities were fatigue, mucositis, hand-foot syndrome, diarrhea, hypertension, and hypothyroidism.
 - Pazopanib. An oral angiogenesis inhibitor targeting VEGFR-1, -2 and -3, PDGFR-alpha and -beta, and c-KIT, pazopanib has shown promise in a phase III trial. Patients with advanced clear-cell RCC (n = 475) with no prior treatment or one prior cytokine-based treatment were randomly assigned 2:1 to receive either pazopanib or placebo. Progression-free survival averaged 9.2 months in the pazopanib group vs 4.2 months in the placebo group.³³ The objective response rate was 30% with pazopanib and 3% with placebo (all results were statistically significant). Common adverse reactions included diarrhea, hypertension, hair-color changes, nausea, anorexia, vomiting, fatigue, abdominal pain, and headache. Hepatotoxicity was notable as a grade 3 toxicity, therefore it is critical to monitor liver function before and during treatment. Pazopanib also has been associated with a prolonged QTc interval.
 - **Bevacizumab.** A monoclonal antibody that binds to and neutralizes circulating VEGF protein,³⁴ bevacizumab plus interferon-alpha has been associated with a 31% objective response rate with a median PFS of 10.2 vs 5.4 months (hazard ratio, 0.63; 95% CI, 0.52-0.75; P = 0.0001) vs interferon-alpha alone. This benefit was observed irrespective of risk group or whether reduced-dose interferon-alpha was given. In the US, a similar trial performed by the Cancer and Leukemia Group B, also demonstrated a PFS advantage in patients receiving bevacizumab. There was significantly more grade 3 to 4 hypertension, anorexia, fatigue, and proteinuria in patients receiving bevacizumab plus interferon-alpha. Patients who developed hypertension on bevacizumab plus interferon-alpha had significantly improved PFS and OS vs patients without hypertension.³⁵
 - Sorafenib. A small molecule inhibitor of VEGF and related receptors, sorafenib has been linked to extended PFS in patients with RCC. In a phase III trial, 905 patients with treatment-refractory metastatic RCC were randomly assigned to receive either oral sorafenib 400 mg twice a day or placebo. Patients in the sorafenib group had 5.5 months of PFS vs 2.8 months for those in the placebo group (*P* < 0.0001).³⁶

- Axitinib. A selective, second-generation inhibitor of VEGFR-1, -2, and -3, axitinib is a category 1 recommendation by the NCCN Kidney Cancer Panel in patients in whom 1 prior systemic therapy has failed. The approval was based on a multicenter, randomized phase III study comparing patients treated with axitinib vs sorafenib following first-line therapy with sunitinib, bevacizumab plus interferon-alpha, temsirolimus, or cytokines. The median PFS was 6.7 months for patients who received axitinib compared with 4.7 months in those who received sorafenib (hazard ratio, 0.665; 95% CI, 0.544-0.812; one-sided *P* < 0.0001). Treatment was discontinued because of toxic effects in 14 (4%) of 359 patients treated with axitinib and 29 (8%) of 355 patients treated with sorafenib. The most common adverse events were diarrhea, hypertension, and fatigue in the axitinib arm, and diarrhea, palmar-plantar erythrodysesthesia, and alopecia in the sorafenib arm.³⁷
- b. mTOR inhibitors
 - Temsirolimus. An inhibitor of mTOR, a molecule implicated in several tumor-promoting intracellular signaling pathways, temsirolimus has been included by the NCCN Kidney Cancer Panel as a category 1 recommendation for first-line treatment of patients with poor prognosis and relapsed or medically unresectable, predominantly clear-cell stage IV RCC.³¹ Patients (n = 626) were randomly assigned to temsirolimus 25 mg per week IV vs interferon alone vs temsirolimus 15 mg per week IV plus interferon. Patients treated with temsirolimus had a longer overall survival than those who received interferon monotherapy (10.9 months vs 7.3 months, P = 0.003).³⁸ Adverse events include rash, stomatitis, pain, infection, peripheral edema, thrombocytopenia and neutropenia, hyperlipidemia, hypercholesterolemia, and hyperglycemia.
 - Everolimus. An orally administered inhibitor of mTOR, everolimus is approved as a second-line therapy after treatment with sorafenib or sunitinib has failed.³¹ In the RECORD 1 trial, an international, multicenter, double blind, randomized phase III trial, everolimus was compared with placebo for the treatment of metastatic RCC in patients whose disease had progressed during treatment with sunitinib or sorafenib. Patients (n = 410) were randomly assigned 2:1 to receive either everolimus or placebo. The primary end point was PFS. According to the updated results of this trial, median PFS determined by independent central review was 4.9 months for everolimus vs 1.9 months (95% CI, 1.8-1.9) for placebo.³⁹ Common adverse events include stomatitis, rash, and fatigue. Pneumonitis is an uncommon but serious side effect presenting as dyspnea.

Summary

- Renal cell carcinoma consists of a heterogeneous group of tumors with distinct genetic and metabolic defects, and histopathologic and clinical features.
- In localized disease, partial nephrectomy for small tumors and radical nephrectomy for large tumors continue to be the gold-standard treatments.
- Cytoreductive nephrectomy is often indicated before the start of systemic treatment in appropriately selected patients with metastatic disease.
- Immunotherapy (high-dose IL-2) is mainly reserved for patients with a good prognosis and is administered on the basis of a durable complete response rate.
- Targeted drugs, including inhibitors of VEGF and mTOR, offer new effective therapeutic options for patients with metastatic disease.

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About the Authors:

Namita Chittoria, MD, Fellow, Experimental Therapeutics Department of Solid Tumor Oncology, Cleveland Clinic Taussig Cancer Institute Cleveland Clinic, Cleveland, Ohio

Brian I. Rini, MD, Staff Physician Department of Solid Tumor Oncology, Cleveland Clinic Taussig Cancer Institute Department of Urology, Glickman Urological and Kidney Institute Cleveland Clinic, Cleveland, Ohio

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