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Kidney Cancer JOURNAL

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Emerging Reclassification Schemes of RCC: New Entities Identified

ALSO: Marriage Improves Outcomes in Kidney Cancer

Recapping ASCO 2014: Analysis & Trends

An Educational Service for Medical Oncologists, Hematologist-Oncologists, and Urologists

About the Cover
Light micrograph of a section through a malignant renal neoplasm (round, center) in the renal vein (c-shaped).

KCJ TABLE OF CONTENTS

KCJ EDITOR'S MEMO

Reclassification of Tumor Subtypes Could Offer New Insights into Therapy


Robert Figlin, MD

For the moment, set aside your pre-conceived notions of what generally constitutes prognostic factors in renal cell carcinoma (RCC). The first that come to mind no doubt include TNM stage, Fuhrman's grade, and patient performance status, not necessarily limited to those variables. There is one obviously missing from this list: histology.

If anyone needs much of a reminder about the extent to which histology also should be considered, then review all of the recent articles appearing on undifferentiated and non-conventional RCC and rare tumors. It is part of a significant evolution in the reclassification of RCC as histological classification receives more of the attention it deserves. One might ask whether "undifferentiated" is a term becoming somewhat obsolete as new reports have increasingly characterized pathologic variants heretofore considered elusive.

Yes, when the report comes back from the pathology laboratory and the verdict is undifferentiated there is still a presumptive treatment plan based on an evaluation of other prognostic variables and evidence-based approaches. But before long, given the pace of current research initiatives, more of these non-conventional variants will be better characterized.

Classification schemes for kidney cancer have undergone dramatic changes in the past two decades and more are emerging, based on the review by James Hsieh, MD in this issue of the journal. As Schuch et al[1] pointed out in a recent review in *European Urology*, pathologic variants differ not only in disease biology but also in clinical behavior, prognosis and response to systemic therapy. Thus, in the era of genomic medicine, further refinements in characterization of RCC subtypes will be critical in decision making.

The renewed effort to further characterize RCC subtypes is just one piece of a much larger picture, much of it taking shape at Dr Hsieh's laboratory at Memorial Sloan-Kettering Cancer Center. The research initiatives unfolding

(continued on page 96)

INLYTA® (axitinib)

for the treatment of advanced RCC after failure of one prior systemic therapy

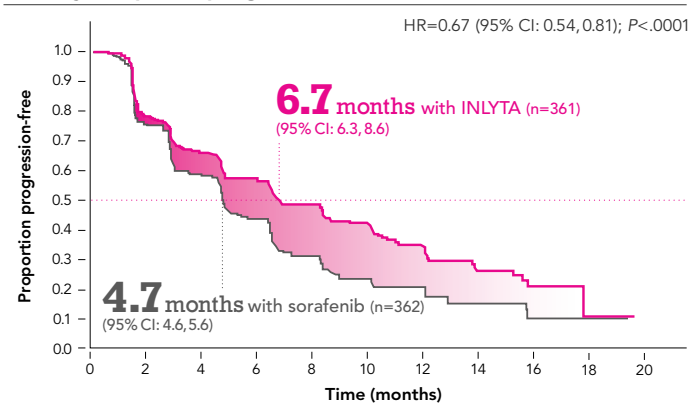
Choose a 2nd-line **treatment** with 2nd-line **evidence**

The ONLY treatment option with superior phase 3 efficacy vs an active comparator, sorafenib, in 2nd-line mRCC*

*Based on MEDLINE® literature review for phase 3 trials in metastatic RCC (mRCC) as of August 2014.

Data are from a multicenter, open-label, phase 3 trial of 723 patients with mRCC after failure of 1st-line therapy (sunitinib-, temsirolimus-, bevacizumab-, or cytokine-containing regimen). Patients were randomized to either INLYTA (5 mg twice daily) or sorafenib (400 mg twice daily) with dose adjustments allowed in both groups. Primary endpoint was PFS. Secondary endpoints included objective response rate, overall survival, and safety and tolerability.[1,2]

Primary endpoint: progression-free survival (PFS)



- **AXIS is the ONLY positive phase 3 trial that was designed to evaluate an exclusively 2nd-line patient population[1†]**

†Based on MEDLINE® literature review for phase 3 trials in mRCC as of August 2014.

- **National Comprehensive Cancer Network® (NCCN®) category 1 recommendation**

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Kidney Cancer include axitinib (INLYTA) as a category 1 recommendation in patients with advanced predominantly clear-cell RCC who have failed one prior systemic therapy[3]

Important Safety Information

- **Hypertension** including **hypertensive crisis** has been observed. Blood pressure should be well controlled prior to initiating INLYTA. Monitor for hypertension and treat as needed. For persistent hypertension, despite use of antihypertensive medications, reduce the dose. Discontinue INLYTA if hypertension is severe and persistent despite use of antihypertensive therapy and dose reduction of INLYTA, and discontinuation should be considered if there is evidence of hypertensive crisis
- **Arterial and venous thrombotic events** have been observed and can be fatal. Use with caution in patients who are at increased risk or who have a history of these events
- **Hemorrhagic events**, including fatal events, have been reported. INLYTA has not been studied in patients with evidence of untreated brain metastasis or recent active gastrointestinal bleeding and should not be used in those patients. If any bleeding requires medical intervention, temporarily interrupt the INLYTA dose
- **Cardiac failure** has been observed and can be fatal. Monitor for signs or symptoms of cardiac failure throughout treatment with INLYTA. Management of cardiac failure may require permanent discontinuation of INLYTA
- **Gastrointestinal perforation and fistula**, including death, have occurred. Use with caution in patients at risk for gastrointestinal perforation or fistula. Monitor for symptoms of gastrointestinal perforation or fistula periodically throughout treatment
- **Hypothyroidism** requiring thyroid hormone replacement has been reported. Monitor thyroid function before initiation of, and periodically throughout, treatment
- No formal studies of the effect of INLYTA on **wound healing** have been conducted. Stop INLYTA at least 24 hours prior to scheduled surgery
- **Reversible Posterior Leukoencephalopathy Syndrome (RPLS)** has been observed. If signs or symptoms occur, permanently discontinue treatment
- Monitor for **proteinuria** before initiation of, and periodically throughout, treatment. For moderate to severe proteinuria, reduce the dose or temporarily interrupt treatment
- **Liver enzyme elevation** has been observed during treatment with INLYTA. Monitor ALT, AST, and bilirubin before initiation of, and periodically throughout, treatment
- For patients with moderate **hepatic impairment**, the starting dose should be decreased. INLYTA has not been studied in patients with severe hepatic impairment
- Women of childbearing potential should be advised of potential hazard to the fetus and to avoid becoming **pregnant** while receiving INLYTA
- Avoid strong **CYP3A4/5 inhibitors**. If unavoidable, reduce the dose. Grapefruit or grapefruit juice may also increase INLYTA plasma concentrations and should be avoided
- Avoid strong **CYP3A4/5 inducers** and, if possible, avoid moderate CYP3A4/5 inducers
- The **most common (≥20%) adverse events (AEs)** occurring in patients receiving INLYTA (all grades, vs sorafenib) were diarrhea, hypertension, fatigue, decreased appetite, nausea, dysphonia, hand-foot syndrome, weight decreased, vomiting, asthenia, and constipation
- The **most common (≥10%) grade 3/4 AEs** occurring in patients receiving INLYTA (vs sorafenib) were hypertension, diarrhea, and fatigue
- The **most common (≥20%) lab abnormalities** occurring in patients receiving INLYTA (all grades, vs sorafenib) included increased creatinine, decreased bicarbonate, hypocalcemia, decreased hemoglobin, decreased lymphocytes (absolute), increased ALP, hyperglycemia, increased lipase, increased amylase, increased ALT, and increased AST

Please see brief summary on the following pages.

Inlyta® axitinib 1mg and 5mg tablets

INLYTA® (AXITINIB) TABLETS FOR ORAL ADMINISTRATION
Initial U.S. Approval: 2012

Brief Summary of Prescribing Information

INDICATIONS AND USAGE: INLYTA is indicated for the treatment of advanced renal cell carcinoma (RCC) after failure of one prior systemic therapy.

DOSAGE AND ADMINISTRATION

Recommended Dosing. The recommended starting oral dose of INLYTA is 5 mg twice daily. Administer INLYTA doses approximately 12 hours apart with or without food. INLYTA should be swallowed whole with a glass of water.

If the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time.

Dose Modification Guidelines. Dose increase or reduction is recommended based on individual safety and tolerability.

Over the course of treatment, patients who tolerate INLYTA for at least two consecutive weeks with no adverse reactions >Grade 2 (according to the Common Toxicity Criteria for Adverse Events [CTCAE]), are normotensive, and are not receiving anti-hypertension medication, may have their dose increased. When a dose increase from 5 mg twice daily is recommended, the INLYTA dose may be increased to 7 mg twice daily, and further to 10 mg twice daily using the same criteria.

Over the course of treatment, management of some adverse drug reactions may require temporary interruption or permanent discontinuation and/or dose reduction of INLYTA therapy *[see Warnings and Precautions]*. If dose reduction from 5 mg twice daily is required, the recommended dose is 3 mg twice daily. If additional dose reduction is required, the recommended dose is 2 mg twice daily.

Strong CYP3A4/5 Inhibitors: The concomitant use of strong CYP3A4/5 inhibitors should be avoided (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole). Selection of an alternate concomitant medication with no or minimal CYP3A4/5 inhibition potential is recommended. Although INLYTA dose adjustment has not been studied in patients receiving strong CYP3A4/5 inhibitors, if a strong CYP3A4/5 inhibitor must be co-administered, a dose decrease of INLYTA by approximately half is recommended, as this dose reduction is predicted to adjust the axitinib area under the plasma concentration vs time curve (AUC) to the range observed without inhibitors. The subsequent doses can be increased or decreased based on individual safety and tolerability. If co-administration of the strong inhibitor is discontinued, the INLYTA dose should be returned (after 3–5 half-lives of the inhibitor) to that used prior to initiation of the strong CYP3A4/5 inhibitor.

Hepatic Impairment: No starting dose adjustment is required when administering INLYTA to patients with mild hepatic impairment (Child-Pugh class A). Based on the pharmacokinetic data, the INLYTA starting dose should be reduced by approximately half in patients with baseline moderate hepatic impairment (Child-Pugh class B). The subsequent doses can be increased or decreased based on individual safety and tolerability. INLYTA has not been studied in patients with severe hepatic impairment (Child-Pugh class C).

DOSAGE FORMS AND STRENGTHS

1 mg tablets of INLYTA: red, film-coated, oval tablets, debossed with "Pfizer" on one side and "1 XNB" on the other side.

5 mg tablets of INLYTA: red, film-coated, triangular tablets, debossed with "Pfizer" on one side and "5 XNB" on the other side.

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS

Hypertension and Hypertensive Crisis. In a controlled clinical study with INLYTA for the treatment of patients with RCC, hypertension was reported in 145/359 patients (40%) receiving INLYTA and 103/355 patients (29%) receiving sorafenib. Grade 3/4 hypertension was observed in 56/359 patients (16%) receiving INLYTA and 39/355 patients (11%) receiving sorafenib. Hypertensive crisis was reported in 2/359 patients (<1%) receiving INLYTA and none of the patients receiving sorafenib. The median onset time for hypertension (systolic blood pressure >150 mmHg or diastolic blood pressure >100 mmHg) was within the first month of the start of INLYTA treatment and blood pressure increases have been observed as early as 4 days after starting INLYTA. Hypertension was managed with standard antihypertensive therapy. Discontinuation of INLYTA treatment due to hypertension occurred in 1/359 patients (<1%) receiving INLYTA and none of the patients receiving sorafenib.

Blood pressure should be well-controlled prior to initiating INLYTA. Patients should be monitored for hypertension and treated as needed with standard anti-hypertensive therapy. In the case of persistent hypertension despite use of anti-hypertensive medications, reduce the INLYTA dose. Discontinue INLYTA if hypertension is severe and persistent despite anti-hypertensive therapy and dose reduction of INLYTA, and discontinuation should be considered if there is evidence of hypertensive crisis. If INLYTA is interrupted, patients receiving antihypertensive medications should be monitored for hypotension.

Arterial Thromboembolic Events. In clinical trials, arterial thromboembolic events have been reported, including deaths. In a controlled clinical study with INLYTA for the treatment of patients with RCC, Grade 3/4 arterial thromboembolic events were reported in 4/359 patients (1%) receiving INLYTA and 4/355 patients (1%) receiving sorafenib. Fatal cerebrovascular accident was reported in 1/359 patients (<1%) receiving INLYTA and none of the patients receiving sorafenib *[see Adverse Reactions]*.

In clinical trials with INLYTA, arterial thromboembolic events (including transient ischemic attack, cerebrovascular accident, myocardial infarction, and retinal artery occlusion) were reported in 17/715 patients (2%), with two deaths secondary to cerebrovascular accident.

Use INLYTA with caution in patients who are at risk for, or who have a history of, these events. INLYTA has not been studied in patients who had an arterial thromboembolic event within the previous 12 months.

Venous Thromboembolic Events. In clinical trials, venous thromboembolic events have been reported, including deaths. In a controlled clinical study with INLYTA for the treatment of patients with RCC, venous thromboembolic events were reported in 11/359 patients (3%) receiving INLYTA and 2/355 patients (1%) receiving sorafenib. Grade 3/4 venous thromboembolic events were reported in 9/359 patients (3%) receiving INLYTA (including pulmonary embolism, deep vein thrombosis, retinal vein occlusion and retinal vein thrombosis) and 2/355 patients (1%) receiving sorafenib. Fatal pulmonary embolism was reported in 1/359 patients (<1%) receiving INLYTA and none of the patients receiving sorafenib. In clinical trials with INLYTA, venous thromboembolic events were reported in 22/715 patients (3%), with two deaths secondary to pulmonary embolism.

Use INLYTA with caution in patients who are at risk for, or who have a history of, these events. INLYTA has not been studied in patients who had a venous thromboembolic event within the previous 6 months.

Hemorrhage. In a controlled clinical study with INLYTA for the treatment of patients with RCC, hemorrhagic events were reported in 58/359 patients (16%) receiving INLYTA and 64/355 patients (18%) receiving sorafenib. Grade 3/4 hemorrhagic events were reported in 5/359 (1%) patients receiving INLYTA (including cerebral hemorrhage, hematuria, hemoptysis, lower gastrointestinal hemorrhage, and melena) and 11/355 (3%) patients receiving sorafenib. Fatal hemorrhage was reported in 1/359 patients (<1%) receiving INLYTA (gastric hemorrhage) and 3/355 patients (1%) receiving sorafenib.

INLYTA has not been studied in patients who have evidence of untreated brain metastasis or recent active gastrointestinal bleeding and should not be used in those patients. If any bleeding requires medical intervention, temporarily interrupt the INLYTA dose.

Cardiac Failure. In a controlled clinical study with INLYTA for the treatment of patients with RCC, cardiac failure was reported in 6/359 patients (2%) receiving INLYTA and 3/355 patients (1%) receiving sorafenib. Grade 3/4 cardiac failure was observed in 2/359 patients (1%) receiving INLYTA and 1/355 patients (<1%) receiving sorafenib. Fatal cardiac failure was reported in 2/359 patients (1%) receiving INLYTA and 1/355 patients (<1%) receiving sorafenib. Monitor for signs or symptoms of cardiac failure throughout treatment with INLYTA. Management of cardiac failure may require permanent discontinuation of INLYTA.

Gastrointestinal Perforation and Fistula Formation. In a controlled clinical study with INLYTA for the treatment of patients with RCC, gastrointestinal perforation was reported in 1/359 patients (<1%) receiving INLYTA and none of the patients receiving sorafenib. In clinical trials with INLYTA, gastrointestinal perforation was reported in 5/715 patients (1%), including one death. In addition to cases of gastrointestinal perforation, fistulas were reported in 4/715 patients (1%).

Monitor for symptoms of gastrointestinal perforation or fistula periodically throughout treatment with INLYTA.

Thyroid Dysfunction. In a controlled clinical study with INLYTA for the treatment of patients with RCC, hypothyroidism was reported in 69/359 patients (19%) receiving INLYTA and 29/355 patients (8%) receiving sorafenib. Hyperthyroidism was reported in 4/359 patients (1%) receiving INLYTA and 4/355 patients (1%) receiving sorafenib. In patients who had thyroid stimulating hormone (TSH) <5 μU/mL before treatment, elevations of TSH to ≥10 μU/mL occurred in 79/245 patients (32%) receiving INLYTA and 25/232 patients (11%) receiving sorafenib.

Monitor thyroid function before initiation of, and periodically throughout, treatment with INLYTA. Treat hypothyroidism and hyperthyroidism according to standard medical practice to maintain euthyroid state.

Wound Healing Complications. No formal studies of the effect of INLYTA on wound healing have been conducted.

Stop treatment with INLYTA at least 24 hours prior to scheduled surgery. The decision to resume INLYTA therapy after surgery should be based on clinical judgment of adequate wound healing.

Reversible Posterior Leukoencephalopathy Syndrome. In a controlled clinical study with INLYTA for the treatment of patients with RCC, reversible posterior leukoencephalopathy syndrome (RPLS) was reported in 1/359 patients (<1%) receiving INLYTA and none of the patients receiving sorafenib. There were two additional reports of RPLS in other clinical trials with INLYTA.

RPLS is a neurological disorder which can present with headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging is necessary to confirm the diagnosis of RPLS. Discontinue INLYTA in patients developing RPLS. The safety of reinitiating INLYTA therapy in patients previously experiencing RPLS is not known.

Proteinuria. In a controlled clinical study with INLYTA for the treatment of patients with RCC, proteinuria was reported in 39/359 patients (11%) receiving INLYTA and 26/355 patients (7%) receiving sorafenib. Grade 3 proteinuria was reported in 11/359 patients (3%) receiving INLYTA and 6/355 patients (2%) receiving sorafenib.

Monitoring for proteinuria before initiation of, and periodically throughout, treatment with INLYTA is recommended. For patients who develop moderate to severe proteinuria, reduce the dose or temporarily interrupt INLYTA treatment.

Elevation of Liver Enzymes. In a controlled clinical study with INLYTA for the treatment of patients with RCC, alanine aminotransferase (ALT) elevations of all grades occurred in 22% of patients on both arms, with Grade 3/4 events in <1% of patients on the INLYTA arm and 2% of patients on the sorafenib arm.

Monitor ALT, aspartate aminotransferase (AST) and bilirubin before initiation of and periodically throughout treatment with INLYTA.

Hepatic Impairment. The systemic exposure to axitinib was higher in subjects with moderate hepatic impairment (Child-Pugh class B) compared to subjects with normal hepatic function. A dose decrease is recommended when administering INLYTA to patients with moderate hepatic impairment (Child-Pugh class B). INLYTA has not been studied in patients with severe hepatic impairment (Child-Pugh class C).

Pregnancy. INLYTA can cause fetal harm when administered to a pregnant woman based on its mechanism of action. There are no adequate and well-controlled studies in pregnant women using INLYTA. In developmental toxicity studies in mice, axitinib was teratogenic, embryotoxic and fetotoxic at maternal exposures that were lower than human exposures at the recommended clinical dose.

Women of childbearing potential should be advised to avoid becoming pregnant while receiving INLYTA. If this drug is used during pregnancy, or if a patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus.

ADVERSE REACTIONS

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

The safety of INLYTA has been evaluated in 715 patients in monotherapy studies, which included 537 patients with advanced RCC. The data described reflect exposure to INLYTA in 359 patients with advanced RCC who participated in a randomized clinical study versus sorafenib.

The following risks, including appropriate action to be taken, are discussed in greater detail in other sections of the label: hypertension, arterial thromboembolic events, venous thromboembolic events, hemorrhage, gastrointestinal perforation and fistula formation, thyroid dysfunction, wound healing complications, RPLS, proteinuria, elevation of liver enzymes, and fetal development.

Clinical Trials Experience. The median duration of treatment was 6.4 months (range 0.03 to 22.0) for patients who received INLYTA and 5.0 months (range 0.03 to 20.1) for patients who received sorafenib. Dose modifications or temporary delay of treatment due to an adverse reaction occurred in 199/359 patients (55%) receiving INLYTA and 220/355 patients (62%) receiving sorafenib. Permanent discontinuation due to an adverse reaction occurred in 34/359 patients (9%) receiving INLYTA and 46/355 patients (13%) receiving sorafenib.

The most common (≥20%) adverse reactions observed following treatment with INLYTA were diarrhea, hypertension, fatigue, decreased appetite, nausea, dysphonia, palmar-plantar erythrodysesthesia (hand-foot) syndrome, weight decreased, vomiting, asthenia, and constipation.

The following table presents adverse reactions reported in ≥10% patients who received INLYTA or sorafenib.

Adverse Reactions Occurring in ≥10% of Patients Who Received INLYTA or Sorafenib

Adverse Reaction[a]	INLYTA (N=359)		Sorafenib (N=355)	
	All Grades[b]	Grade 3/4	All Grades[b]	Grade 3/4
	%	%	%	%
Diarrhea	55	11	53	7
Hypertension	40	16	29	11
Fatigue	39	11	32	5
Decreased appetite	34	5	29	4
Nausea	32	3	22	1
Dysphonia	31	0	14	0
Palmar-plantar erythrodysesthesia syndrome	27	5	51	16
Weight decreased	25	2	21	1
Vomiting	24	3	17	1
Asthenia	21	5	14	3
Constipation	20	1	20	1
Hypothyroidism	19	<1	8	0
Cough	15	1	17	1
Mucosal inflammation	15	1	12	1
Arthralgia	15	2	11	1
Stomatitis	15	1	12	<1
Dyspnea	15	3	12	3
Abdominal pain	14	2	11	1
Headache	14	1	11	0
Pain in extremity	13	1	14	1
Rash	13	<1	32	4
Proteinuria	11	3	7	2
Dysgeusia	11	0	8	0
Dry skin	10	0	11	0
Dyspepsia	10	0	2	0
Pruritus	7	0	12	0
Alopecia	4	0	32	0
Erythema	2	0	10	<1

[a]Percentages are treatment-emergent, all-causality events

[b]National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0

Selected adverse reactions (all grades) that were reported in <10% of patients treated with INLYTA included dizziness (9%), upper abdominal pain (8%), myalgia (7%), dehydration (6%), epistaxis (6%), anemia (4%), hemorrhoids (4%), hematuria (3%), tinnitus (3%), lipase increased (3%), glossodynia (3%), pulmonary embolism (2%), rectal hemorrhage (2%), hemoptysis (2%), deep vein thrombosis (1%), retinal-vein occlusion/thrombosis (1%), polycythemia (1%), and transient ischemic attack (1%).

The following table presents the most common laboratory abnormalities reported in ≥10% patients who received INLYTA or sorafenib.

Laboratory Abnormalities Occurring in ≥10% of Patients Who Received INLYTA or Sorafenib

Laboratory Abnormality	N	INLYTA		N	Sorafenib	
		All Grades[a]	Grade 3/4		All Grades[a]	Grade 3/4
		%	%		%	%
Hematology						
Hemoglobin decreased	320	35	<1	316	52	4
Lymphocytes (absolute) decreased	317	33	3	309	36	4
Platelets decreased	312	15	<1	310	14	0
White blood cells decreased	320	11	0	315	16	<1
Chemistry						
Creatinine increased	336	55	0	318	41	<1
Bicarbonate decreased	314	44	<1	291	43	0
Hypocalcemia	336	39	1	319	59	2
ALP increased	336	30	1	319	34	1
Hyperglycemia	336	28	2	319	23	2
Lipase increased	338	27	5	319	46	15
Amylase increased	338	25	2	319	33	2
ALT increased	331	22	<1	313	22	2
AST increased	331	20	<1	311	25	1
Hypernatremia	338	17	1	319	13	1
Hypoalbuminemia	337	15	<1	319	18	1
Hyperkalemia	333	15	3	314	10	3
Hypoglycemia	336	11	<1	319	8	<1
Hyponatremia	338	13	4	319	11	2
Hypophosphatemia	336	13	2	318	49	16

[a]National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase

Selected laboratory abnormalities (all grades) that were reported in <10% of patients treated with INLYTA included hemoglobin increased (above the upper limit of normal) (9% for INLYTA versus 1% for sorafenib) and hypercalcemia (6% for INLYTA versus 2% for sorafenib).

DRUG INTERACTIONS

In vitro data indicate that axitinib is metabolized primarily by CYP3A4/5 and, to a lesser extent, CYP1A2, CYP2C19, and uridine diphosphate-glucuronosyltransferase (UGT) 1A1.

CYP3A4/5 Inhibitors. Co-administration of ketoconazole, a strong inhibitor of CYP3A4/5, increased the plasma exposure of axitinib in healthy volunteers. Co-administration of INLYTA with strong CYP3A4/5 inhibitors should be avoided. Grapefruit or grapefruit juice may also increase axitinib plasma concentrations and should be avoided. Selection of concomitant medication with no or minimal CYP3A4/5 inhibition potential is recommended. If a strong CYP3A4/5 inhibitor must be coadministered, the INLYTA dose should be reduced *[see Dosage and Administration]*.

CYP3A4/5 Inducers. Co-administration of rifampin, a strong inducer of CYP3A4/5, reduced the plasma exposure of axitinib in healthy volunteers. Co-administration of INLYTA with strong CYP3A4/5 inducers (e.g., rifampin, dexamethasone, phenytoin, carbamazepine, rifabutin, rifapentin, phenobarbital, and St. John's wort) should be avoided. Selection of concomitant medication with no or minimal CYP3A4/5 induction potential is recommended *[see Dosage and Administration]*. Moderate CYP3A4/5 inducers (e.g., bosentan, efavirenz, etravirine, modafinil, and nafcillin) may also reduce the plasma exposure of axitinib and should be avoided if possible.

USE IN SPECIFIC POPULATIONS

Pregnancy. Pregnancy Category D *[see Warnings and Precautions]*.

There are no adequate and well-controlled studies with INLYTA in pregnant women. INLYTA can cause fetal harm when administered to a pregnant woman based on its mechanism of action. Axitinib was teratogenic, embryotoxic and fetotoxic in mice at exposures lower than human exposures at the recommended starting dose. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus.

Oral axitinib administered twice daily to female mice prior to mating and through the first week of pregnancy caused an increase in post-implantation loss at all doses tested (≥15 mg/kg/dose, approximately 10 times the systemic exposure (AUC) in patients at the recommended starting dose).

In an embryo-fetal developmental toxicity study, pregnant mice received oral doses of 0.15, 0.5 and 1.5 mg/kg/dose axitinib twice daily during the period of organogenesis. Embryo-fetal toxicities observed in the absence of maternal toxicity included malformation (cleft palate) at 1.5 mg/kg/dose (approximately 0.5 times the AUC in patients at the recommended starting dose) and variation in skeletal ossification at ≥0.5 mg/kg/dose (approximately 0.15 times the AUC in patients at the recommended starting dose).

Nursing Mothers. It is not known whether axitinib is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from INLYTA, 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.

Pediatric Use. The safety and efficacy of INLYTA in pediatric patients have not been studied.

Toxicities in bone and teeth were observed in immature mice and dogs administered oral axitinib twice daily for 1 month or longer. Effects in bone consisted of thickened growth plates in mice and dogs at ≥15 mg/kg/dose (approximately 6 and 15 times, respectively, the systemic exposure (AUC) in patients at the recommended starting dose). Abnormalities in growing incisor teeth (including dental caries, malocclusions and broken and/or missing teeth) were observed in mice administered oral axitinib twice daily at ≥5 mg/kg/dose (approximately 1.5 times the AUC in patients at the recommended starting dose). Other toxicities of potential concern to pediatric patients have not been evaluated in juvenile animals.

Geriatric Use. In a controlled clinical study with INLYTA for the treatment of patients with RCC, 123/359 patients (34%) treated with INLYTA were ≥65 years of age. Although greater sensitivity in some older individuals cannot be ruled out, no overall differences were observed in the safety and effectiveness of INLYTA between patients who were ≥65 years of age and younger.

No dosage adjustment is required in elderly patients.

Hepatic Impairment. In a dedicated hepatic impairment trial, compared to subjects with normal hepatic function, systemic exposure following a single dose of INLYTA was similar in subjects with baseline mild hepatic impairment (Child-Pugh class A) and higher in subjects with baseline moderate hepatic impairment (Child-Pugh class B).

No starting dose adjustment is required when administering INLYTA to patients with mild hepatic impairment (Child-Pugh class A). A starting dose decrease is recommended when administering INLYTA to patients with moderate hepatic impairment (Child-Pugh class B).

INLYTA has not been studied in subjects with severe hepatic impairment (Child-Pugh class C).

Renal Impairment. No dedicated renal impairment trial for axitinib has been conducted. Based on the population pharmacokinetic analyses, no significant difference in axitinib clearance was observed in patients with pre-existing mild to severe renal impairment (15 mL/min ≤creatinine clearance [CLcr] <89 mL/min). No starting dose adjustment is needed for patients with pre-existing mild to severe renal impairment. Caution should be used in patients with end-stage renal disease (CLcr <15 mL/min).

OVERDOSAGE

There is no specific treatment for INLYTA overdose.

In a controlled clinical study with INLYTA for the treatment of patients with RCC, 1 patient inadvertently received a dose of 20 mg twice daily for 4 days and experienced dizziness (Grade 1).

In a clinical dose finding study with INLYTA, subjects who received starting doses of 10 mg twice daily or 20 mg twice daily experienced adverse reactions which included hypertension, seizures associated with hypertension, and fatal hemoptysis.

In cases of suspected overdose, INLYTA should be withheld and supportive care instituted.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility. Carcinogenicity studies have not been conducted with axitinib.

Axitinib was not mutagenic in an *in vitro* bacterial reverse mutation (Ames) assay and was not clastogenic in the *in vitro* human lymphocyte chromosome aberration assay. Axitinib was genotoxic in the *in vivo* mouse bone marrow micronucleus assay.

INLYTA has the potential to impair reproductive function and fertility in humans. In repeat-dose toxicology studies, findings in the male reproductive tract were observed in the testes/epididymis (decreased organ weight, atrophy or degeneration, decreased numbers of germinal cells, hypospermia or abnormal sperm forms, reduced sperm density and count) at ≥15 mg/kg/dose administered orally twice daily in mice (approximately 7 times the systemic exposure (AUC) in patients at the recommended starting dose) and ≥1.5 mg/kg/dose administered orally twice daily in dogs (approximately 0.1 times the AUC in patients at the recommended starting dose). Findings in the female reproductive tract in mice and dogs included signs of delayed sexual maturity, reduced or absent corpora lutea, decreased uterine weights and uterine atrophy at ≥5 mg/kg/dose (approximately 1.5 or 0.3 times the AUC in patients at the recommended starting dose compared to mice and dogs, respectively).

In a fertility study in mice, axitinib did not affect mating or fertility rate when administered orally twice daily to males at any dose tested up to 50 mg/kg/dose following at least 70 days of administration (approximately 57 times the AUC in patients at the recommended starting dose). In female mice, reduced fertility and embryonic viability were observed at all doses tested (≥15 mg/kg/dose administered orally twice daily) following at least 15 days of treatment with axitinib (approximately 10 times the AUC in patients at the recommended starting dose).

PATIENT COUNSELING INFORMATION

Reversible Posterior Leukoencephalopathy Syndrome. Advise patients to inform their doctor if they have worsening of neurological function consistent with RPLS (headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances).

Pregnancy. Advise patients that INLYTA may cause birth defects or fetal loss and that they should not become pregnant during treatment with INLYTA. Both male and female patients should be counseled to use effective birth control during treatment with INLYTA. Female patients should also be advised against breast-feeding while receiving INLYTA.

Concomitant Medications. Advise patients to inform their doctor of all concomitant medications, vitamins, or dietary and herbal supplements.

Rx only August 2014

References: 1. Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomized phase 3 trial. *Lancet*. 2011;378(9807):1931-1939. **2.** Data on file. Pfizer Inc, New York, NY. **3.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Kidney Cancer V.3.2014. © National Comprehensive Cancer Network, Inc 2014. All rights reserved. Accessed July 1, 2014. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

mRCC=metastatic renal cell carcinoma; ORR=objective response rate; OS=overall survival; PFS=progression-free survival.

Essential Peer-Reviewed Reading in Kidney Cancer

The peer-reviewed articles summarized in this section were selected by the Editor-in-Chief, Robert A. Figlin, MD, for their timeliness, importance, relevance, and potential impact on clinical practice or translational research.

Contemporary incidence and mortality rates of kidney cancer in the United States. Gandaglia G, Ravi P, Abdollah F, et al. *Can Urol Ass J*. 2014;8:247-252

Summary: These authors computed age-adjusted incidence, mortality rates and 5-year cancer-specific survival (CSS) for patients with histologically confirmed kidney cancer between 1975 and 2009. Long-term (1975–2009) and short-term (2000–2009) trends were examined by joinpoint analysis, and quantified using the annual percent change (APC). The reported findings were stratified according to disease stage. Age-adjusted incidence rates of RCC increased by +2.76%/year between 1975 and 2009 (from 6.5 to 17.1/100 000 person years, $P< 0.001$), and by +2.85%/year between 2000 and 2009 ($P < 0.001$). For the same time points, the corresponding APC for the incidence of localized stage were +4.55%/year (from 3.0 to 12.2/100 000 person years, $P< 0.001$), and +4.42%/year ($P< 0.001$), respectively. The incidence rates of regional stage increased by +0.88%/year between 1975 and 2009 ($P< 0.001$), but stabilized in recent years (2000–2009: +0.56%/year, p = 0.4). Incidence rates of distant stage remained unchanged in long- and short-term trends. Overall mortality rates increased by +1.72%/year between 1975 and 2009 (from 1.2 to 5.0/100 000 person-years, $P<0.001$), but stabilized between 1994 and 2004 ($P = 0.1$). Short-term mortality rates increased in a significant fashion by +3.14%/year only for localized stage ($P< 0.001$).

Conclusion: This is a timely update of incidence and mortality for RCC in the US, relying on the Surveillance, Epidemiology, and End Results (SEER) database. Mortality rates overall increased by nearly 2%/year for a 35-year period studied but stabilized in more recent years. Short-term mortality rates (2000-2009) increased by about 3%/year but only for localized RCC.

Circulating 25-hydroxyvitamin D_3 in relation to renal cell carcinoma incidence and survival in the EPIC cohort. Muller DC, Fanidi A, Midttun Ø, et al. *Am J Epidemiol*. (2014) Sep 8; [Epub ahead of print],

Summary: Normal renal function is essential for vitamin D metabolism, but it is unclear whether circulating vitamin D is associated with risk of renal cell carcinoma (RCC). This study assessed whether 25-hydroxyvitamin D_3 ($25(OH)D_3$) was associated with risk of RCC and death after RCC diagnosis in the European Prospective Investigation into Cancer and Nutrition (EPIC). EPIC recruited 385,747 participants with blood samples between 1992 and 2000. The current study included 560 RCC cases, 557 individually matched controls, and 553 additional controls. Circulating $25(OH)D_3$ was assessed by mass spectrometry.

Conclusion: A doubling of $25(OH)D_3$ was associated with 28% lower odds of RCC after adjustment for season of and age at blood collection, sex, and country of recruitment (odds ratio = 0.72, $P = 0.0004$). This estimate was attenuated somewhat after additional adjustment for smoking status at baseline, circulating cotinine, body mass index (weight (kg)/height $(m)^2$), and alcohol intake (odds ratio = 0.82, $P = 0.038$). There was also some indication that both low and high $25(OH)D_3$ levels were associated with higher risk of death from any cause among RCC cases.

Sequential immune monitoring in patients with melanoma and renal cell carcinoma treated with high-dose interleukin-2: immune patterns and correlation with outcome. Foureau DM, Amin A, White RL, et al. *Cancer Immunol/Immunother*. 2014;Sep 10 [Epub ahead of print].

Summary: Interleukin-2 (IL-2) therapy leads to clinically relevant responses in 10-16 % of patients with metastatic melanoma (MMEL) or 10-30 % of patients with metastatic renal cell carcinoma (MRCC). To date, no biomarkers have been validated to identify patients who are likely to respond. The hypothesis here is that changes in T cell subset distribution in patients undergoing IL-2 therapy may correlate with treatment outcomes. Immune profiles of 64 patients (27-MMEL, 37-MRCC) were evaluated using flow cytometry at baseline, during (≥three doses) and at the end of treatment cycle (30 ± 6 h after last dose), through two courses of IL-2 therapy. Changes in distribution and phenotype of circulating CD4 and CD8 lymphocyte subsets were compared (1) based on cancer types and (2) intra-patient during the course of the IL-2 therapy. Exploratory analysis of immunologic profiles was also performed based on treatment outcome.

Conclusion: Independent of cancer type, IL-2 led to a transient decrease of circulating effector lymphocytes, while regulatory T cells gradually increased. Interleukin-2 differentially affected a subset of CD8 T cell expressing Foxp3, depending on malignancy type. In MMEL patients, IL-2 gradually expanded circulating CD8 Foxp3+ cells; in MRCC patients, IL-2 transiently increased expression of CD103 and CCR4 homing markers. Monitoring of adaptive immune variables early on and during the course of IL-2 therapy revealed transient alterations in immune profiles, specific to MMEL and MRCC patients, related to immune balance (and ultimately response to IL-2 therapy) or T cell egress from the circulation.

PD-L1 Expression in Non-clear cell Renal Cell Carcinoma. Choueiri TK, Fay AP, Gray KP, et al. *Ann Oncol*. 2014;Sep 5 [Epub ahead of print].

Summary: Program Death Ligand-1 (PD-L1) expression in non-clear cell RCC (non-ccRCC) and its association with clinical outcomes are unknown. Formalin-fixed paraffin-embedded (FFPE) specimens were obtained from 101 pa-

(continued on page 104)

Kidney Cancer Journal Author Guidelines

Scope of Manuscripts

The *Kidney Cancer Journal* considers the following types of manuscripts for publication:

- Reviews that summarize and synthesize peer-reviewed literature to date on relevant topics in a scholarly fashion and format.
- Original contributions based on original, basic, clinical, translational, epidemiological, or prevention studies relating to kidney cancer that are well documented, novel, and significant.
- Letters to the Editor on timely and relevant subjects pertaining to the diagnosis and treatment of renal cell carcinoma.
- Clinical case studies.

Manuscript Submission

Authors are required to submit their manuscripts in an electronic format, preferably by email to the Editor-in-Chief, Robert A. Figlin, MD, at rfiglin@coh.org. Please provide in a word processing program. Images should be submitted electronically as well.

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Contact information

List all authors, including mailing address, titles and affiliations, phone, fax, and email. Please note corresponding author.

Peer Review and Editing

Manuscripts will be peer reviewed. Accepted manuscripts will be edited for clarity, spelling, punctuation, grammar, and consistency with American Medical Association (AMA) style. Authors whose manuscripts are not initially accepted may have the opportunity to revise the manuscript based on recommendations from peer reviewers and at the discretion of the Editor-in-Chief.

Conflict of Interest

Kidney Cancer Journal policy requires that authors reveal to the Editor-in-Chief any relationships that they believe could be construed as resulting in an actual, potential, or apparent conflict of interest with regard to the manuscript submitted for review. Authors must disclose this information in the covering letter accompanying their submission.

Manuscript Preparation

Length: Full-length manuscripts should not exceed 4000 words, including references. Please limit the reference list to 50 citations. Manuscripts should be accompanied by figures and/or tables. Generally 4-5 figures and 2-3 tables are preferred for each manuscript. Please include a brief description to accompany these items, as well as a legend for all abbreviations. Manuscripts should not contain an abstract but an introduction is recommended.

Spacing: One space after periods. Manuscripts should be double spaced.

References

All submissions should have references that are referred to in the text by superscripted numbers and that conform to AMA style.
Example:
Lewczuk J, Piszko P, Jagas J, et al. Prognostic factors in medically treated patients with chronic pulmonary embolism. *Chest*. 2001;119:818-823.

Copyright

Newsworthy, late-breaking information from Web-based sources, professional societies, and government agencies

13TH International Kidney Cancer Symposium to Convene Oct. 24-25, Targeting Future Directions in RCC

CHICAGO—Bringing together key individuals and representatives from leading laboratories and centers working with renal cell carcinoma, the 13th International Kidney Cancer Symposium seeks to provide a forum for the exchange of ideas and information that will continue to frame directions for future research and treatment. The CME meeting sponsored by the Kidney Cancer Association will be held October 24-25 at the Radisson Blue Acqua Hotel, Chicago.

The objectives of the meeting are:

- Discuss options for operative and minimally invasive management of localized and metastatic renal cell carcinoma
- Evaluate the growing body of knowledge regarding clinical, molecular, genetic, and biologic characteristics of renal cell carcinoma
- Discuss the molecular genetics and biology of renal cancers and assess the effects of targeted therapy for this tumor
- Define research directions of novel agents and combinations and standard of care therapy for metastatic renal cell carcinoma
- Project future surgical and medical directions and research in non metastatic and metastatic disease.

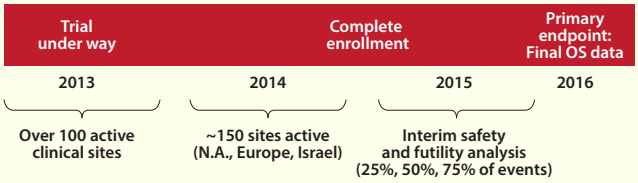
Contact the Kidney Cancer Association for registration and housing information: http://www.kidneycancer.org/knowledge/learn/medical-education-cme/

Enrollment in Argos Therapeutics' Pivotal Phase 3 ADAPT Trial of AGS-003 Surpasses 50%—on Target to Complete Enrollment by Early 2015

DURHAM, NC — Argos Therapeutics, Inc., a biopharmaceutical company focused on development and commercialization of fully personalized immunotherapies for the treatment of cancer and infectious diseases using its Arcelis™ technology platform, HAS announced it has recently surpassed 50% of the target enrollment for the company's ongoing pivotal Phase III ADAPT trial of AGS-003 for the treatment of metastatic renal cell carcinoma (mRCC).

"This is an important milestone for the ADAPT trial as we continue to be pleased with the pace of enrollment and the opportunity to advance this promising, fully personalized immunotherapy in newly diagnosed, synchronous metastatic RCC patients," said Robert A. Figlin, MD, FACP, primary investigator for the ADAPT trial. "We remain encouraged by the potential for AGS-003 to represent an important advance for the immunotherapy field as well as the treatment of advanced RCC in the years ahead."

AGS-003 is an investigational, fully personalized immunotherapy for cancer comprised of autologous tumor RNA-loaded dendritic cells. The ADAPT trial is a randomized, international Phase III trial comparing standard targeted therapy plus AGS-003 to standard therapy alone in 450 mRCC patients. In total, more than 225 patients at more than 120 active ADAPT trial sites have been enrolled and randomized in the trial. In addition, more than 600 patients have participated in the initial tumor collection phase of the trial. The timeline for the ADAPT Trial:



BETHESDA, MD—The FDA has approved the first checkpoint inhibitor, an immune-stimulating drug for melanoma, known as Keytruda. The decision marks the first US approval for a promising new class designed to help the body's own immune system fend off cancer by blocking a protein known as Programmed Death receptor (PD-1), or a related target known as PD-L1, used by tumors to evade disease-fighting cells. Another PD-1 inhibitor is being studied for use in renal cell carcinoma. (*See related story in this issue in the ASCO Highlights.*)

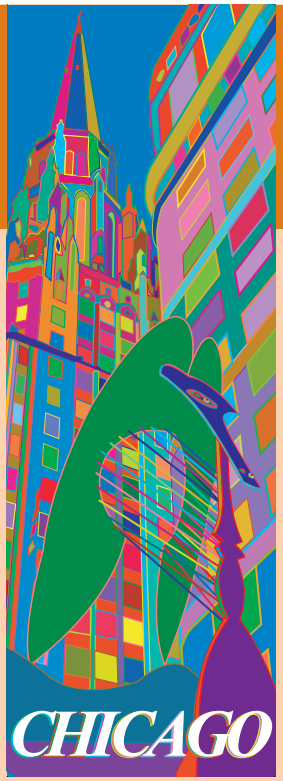
The FDA said clinical trials of Keytruda showed that it shrank tumors in around 24% of patients with advanced melanoma whose disease worsened after prior treatment. The agency had designated the drug a "breakthrough therapy," and approved it nearly two months ahead of an Oct. 28 decision deadline.

Bristol Myers Squibb expects to complete by the end of this year a "rolling" submission for FDA approval of its drug, Opdivo, or nivolumab, for certain patients with late-stage lung cancer. The company also plans to file an FDA application by the end of this month for use of the drug, which is approved in Japan, for patients with advanced melanoma. Favorable results have been reported for the use of this PD-1 inhibitor in kidney cancer as well and a phase 3 trial is ongoing.

Robotic Surgical Ablation Used as Outpatient Tool in RCC

LOS ANGELES—Keck Medical Center of the University of Southern California (USC) is the first medical center in the world to use new robotic technology in an outpatient procedure for a kidney cancer patient.

Urologic surgeons at the USC Institute of Urology, part of Keck Medicine of USC, used the high intensity focused ultrasound (HIFU) surgical ablation system for ablating intra-abdominal tumors. The system enables surgeons to penetrate the abdominal cavity with keyhole cuts to eliminate tumors of four centimeters or less. Inderbir Gill, MD, founding executive director, USC Institute of Urology, and chairman and professor, Catherine and Joseph Aresty Department of Urology at the Keck School of Medicine of USC, performed the surgery on a 62-year-old patient who went home the same day, three to four days less than patients typically experience with kidney cancer surgery. KCJ



Save the Date

Thirteenth International Kidney Cancer Symposium

October 24-25, 2014

Radisson Aqua Blu Hotel, Chicago, Illinois

KidneyCancer.com Cleveland Clinic

www.kidneycancersymposium.com

For more information about the Kidney Cancer Association and about the International Kidney Cancer Symposium in Chicago go to:

www.kidneycancer.com
www.kidneycancersymposium.com

Emerging Reclassification Schemes of RCC: How Identifying New Molecular Entities Among Non-Clear Cell RCC Signifies an Evolution in Managing the Disease

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This is the first of a two-part series on reclassification of renal cell carcinomas (RCCs), many of which are considered non-clear cell RCC (nccRCC). The first part will outline most clinically relevant classifications that should be taken into consideration in treatment planning, and the second part will detail the contemporary genomics information on individual subtypes of kidney cancer. With the evolution of RCC classification, some tumors have an atypical morphology and these tumors often are difficult to categorize in any specific subtype. This report highlights these issues, focuses on how the field is evolving, and what factors need to be considered as part of identifying and characterizing new subtypes. Most importantly, the information emerging from new reports not only crystallizes our understanding of pathologic variants but points toward therapeutic and prognostic opportunities as well.

When each subtype of a tumor harbors a unique biology and responds differently to available treatment strategies, integrated pathologic and molecular classification becomes an all-important consideration. Classification is highly important in RCC for a number of reasons, not the least of which is the implication for selecting appropriate therapies in an era when the spectrum of choices has expanded dramatically. Kidney cancer care has been remarkably reshaped by a series of advances—development of minimally invasive techniques for surgery in the retroperitoneum, emergence of focal therapy, reemergence of percutaneous renal biopsy, introduction of active surveillance strategies, renewed interest in immunotherapy, and the introduction of targeted therapies for patients with advanced disease.[1] The appropriate choice of these can depend on the identification of a variant or phenotype amenable to an evidence-based decision. These more clearly defined subtypes not only allow for a common descriptive language, they help to crystallize the understanding of RCC's molecular origins and its clinical behavior. A robust classification scheme for kidney cancer is important for other reasons: for example, up to 20% of enhancing small renal masses are benign and may not need treatment.[2] Tumors such as papillary adenomas, pure oncocytomas, and angiomyolipomas (except a rare epithelioid variant) do not metastasize.[1] Local symptoms, such as pain or hemorrhage, are rarely associated with these tumors unless they are large, such as >4 cm with angiomyolipomas.

While most of the attention in the clinical literature tends to focus on the evolution of these management approaches in the past, pathobiology-based treatment stratification is at center stage and promises better, effective, personalized care, i.e. tailored treatment plan of individual cancer patients based on tumor morphology, biology, and genetics. This will move current wholesale type clinical trials to smaller yet more targeted trials. Arguably one of the most significant paradigm shifts in the clinical constructs that shape kidney cancer care is the advance in molecular characterization of most kidney cancer subtypes. Current efforts first morphologically group kidney cancer into major subtypes and then perform molecularly characterization for subclassification.[2]

A History Lesson on Classification: Rapid Change, Better Characterization

There has been a rapid evolution in thinking in the pathology community with some of the terms first used in the early 20th century still occasionally used in modern pathology reports. In brief, here is how the knowledge base has grown since the 1980s until now, and within the next few years we are likely to see a new characterization of tumor types that could represent another sea change in our classification schemes.

- Clear cell RCC has long been recognized as the predominant histologic subtype.
- Papillary RCC was better characterized in the 1980s.

Keywords: tumor heterogeneity; reclassification; WHO renal cell carcinoma classification; clear cell renal cell carcinoma; non-clear cell renal cell carcinoma; histological subtypes.

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Table. Common Histologic Renal Cell Carcinoma Subtypes and Their Appearance and Associated Molecular Alterations

Tumor type	Subtype	Gross appearance	Microscopic appearance		Known somatic alterations	Cytogenetic alterations
Clear cell	–	Yellow, well circumscribed, and can possess distinct areas of hemorrhage and necrosis	Abundant clear cytoplasm due to deposition of lipid and glycogen		VHL, PBRM1, SETD2, BAP1, JARID1A, mTOR, PI3K	3p (90%), 14q, 8p, and 9p and gains at 5q and 12q
Papillary	1 2	Mixed cystic/solid consistency. Papillary RCC lesions are often reddish-brown and frequently have a well-demarcated pseudocapsule	Papillary or tubulopapillary architecture. Calcifications, necrosis, and foamy macrophage infiltration.	Type 1: thin, basophilic papillaewith clear cytoplasm Type 2: heterogenous, thicker papillae andeosinophilic cytoplasm.	MET NRF2, CUL3	Gains of 7, 8q, 12q, 16p, 17, 20, and loss of 9p. Papillary type 2 with gains of 8q, loss of 1p and 9p.
Chromophobe	Classic Eosinophilic	Large, well circumscribed, tan-brown tumor with occasional central scar	Distinct cell borders and voluminous cytoplasm, nuclear morphology with perinuclear halos, binucleation	Pale cytoplasm Large tumor cells with fine eosinophilic granules	TP53	Loss of chromosomes 1, 2, 6, 10, 13, and 17
Oncocytoma	–	Mahogany color, well circumscribed, occasional central scar, and rarely with necrosis	Polygonal cell with abundant eosinophilic cytoplasm and uniform, round nuclei		Mitochondrial complex I genes	Loss of 1 p, loss of Y, often normal karyotype
Collecting duct	–	Partially cystic, white-gray appearance and often exhibit invasion into the renal sinus	Tubulopapillary pattern, often with cells taking columnar pattern with hobnail appearance, presence of mucinous material, desmoplastic stroma		Unknown	Losses at 8p, 16p, 1p, 9p, and gains at 13q
Medullary	–	Tan/white, poorly defined capsule, extensive hemorrhage and necrosis	Poorly differentiated, eosinophilic cells; inflammatory infiltative cells; sheet-like or reticular pattern common		Unknown	Poorly described, but believed normal karyotype
MiT family	–	Yellowish tissue often studded by hemorrhage and necrosis	Papillary or nested architecture, granular and eosinophilic cells with voluminous, cytoplasm		–	Recurrent translocations involving Xp11.2 (TFE3) or 6p21(TFEB)

*See Table 1 for known genes/germline mutations associated with each pathologic subtype.
Adapted from: Shuch B, Amin A, Armstrong AJ, et al. Understanding pathologic variants of renal cell carcinoma: distilling therapeutic opportunities from biologic complexity. *Eur Urol*. 2014;http://dx.doi.org/10.1016/j.eururo.2014.04.029.

Kovacs et al[3] reported that these tumors contained more than 75% of papillary features and did not have characteristic 3p chromosomal loss on karyotype analysis. Since that report, two different classes of papillary tumors have been verified.[4]

- Chromophobe RCC, the third most common subtype, was described in the mid-1980s.[5]
- In the 1990s, reports further delineated rare, histologic subtypes, including collecting duct, medullary RCC, translocation RCC, and mucinous tubular and spindle-cell RCC.[6]

Along the way, the widely recognized World Health Organization (WHO) classification of adult renal epithelial neoplasms was introduced in 1998 and then updated in 2004, based on pathology and genetic abnormalities.[7] These classification schemes served as benchmarks for further elucidation of pathological variants. Ten years after the introduction of the 2004 WHO criteria, new efforts seek to redefine the descriptions in this document.

New Initiatives to Revamp the WHO Classification

Until the results of this initiative are presented [*Editor's note: see related article.*], it is useful to examine how far the classification schemes currently applied have clarified various entities and what insights can be gained from modifications proposed in the WHO classification by other groups organized for that purpose. One group providing new direction in the field is the classification working group of the International Society of Urological Pathology (ISUP) with its Vancouver Classification of Renal Neoplasia.[8] Although not yet officially incorporated as part of the WHO scheme, the ISUP produced a consensus that offers a framework for reconsidering existing criteria and how the field is evolving and what new epithelial neoplasms should be recognized. After an exhaustive literature review and a survey of members from numerous international centers such as Johns Hopkins Medical Institutions, Memorial Sloan-Kettering Cancer Center and New York University Medical Center, the working group suggested that 5 entities should be recognized as new distinct epithelial tumors within the WHO classification scheme: (1) tubulocystic RCC; (2) acquired cystic diseae-associated RCC; (3) clear cell (tubule) papillary RCC; (4) the MiT family translocation RCCs (in particular t(6;11), and (5) hereditary leiomyomatosis RCC syndrome-associated RCC. The group also identified 3 rare carcinomas, including Succinate Dehydrogenase B (SDHB) associated RCC, ALK translocation RCC, and on which further study is needed because they are emerging entities.

Overall, some new concepts and modifications were

(continued on page 90)

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 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 experience[1]

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

3x antitumor effect[1-3]

- 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% CI, 4.0-5.5); placebo (n=139): 1.9 months (95% CI, 1.8-1.9) (HR=0.33; 95% CI, 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, nelfinavir, 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.

NOVARTIS ONCOLOGY

AFINITOR® (everolimus) tablets 2.5mg | 5mg | 7.5mg | 10mg

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

8/14 AFI-1095434

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 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 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 ≥ 30%) were stomatitis, infections, asthenia, fatigue, cough, and diarrhea. The most common Grade 3-4 adverse reactions (incidence ≥ 3%) were infections, dyspnea, fatigue, stomatitis, dehydration, pneumonitis, abdominal pain, and asthenia. The most common laboratory abnormalities (incidence ≥ 50%) were anemia, hypercholesterolemia, hypertriglyceridemia, hyperglycemia, lymphopenia, and increased creatinine. The most common Grade 3-4 laboratory abnormalities (incidence ≥ 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 AFINITOR 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 ≥ 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: 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 %
General disorders and administration site conditions						
Asthenia	33	3	<1	23	4	0
Fatigue	31	5	0	27	3	<1
Edema peripheral	25	<1	0	8	<1	0
Pyrexia	20	<1	0	9	0	0
Mucosal inflammation	19	1	0	1	0	0
Respiratory, thoracic and mediastinal disorders						
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 subcutaneous tissue disorders						
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 connective tissue disorders						
Pain in extremity	10	1	0	7	0	0
Median 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, interstitial 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	AFINITOR 10 mg/day N=274			Placebo N=137		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Hematology[a]						
Hemoglobin decreased	92	12	1	79	5	<1
Lymphocytes decreased	51	16	2	28	5	0
Platelets decreased	23	1	0	2	0	<1
Neutrophils decreased	14	0	<1	4	0	0
Clinical chemistry						
Cholesterol increased	77	4	0	35	0	0
Triglycerides 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) increased	25	<1	<1	7	0	0
Alanine transaminase (ALT) increased	21	1	0	4	0	0
Bilirubin increased	3	<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 PgP 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 $AUC_{(0\text{-}inf)}$.

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 ≥ 0.1 mg/kg (0.6 mg/m^2) with resulting exposures of approximately 4% of the exposure ($AUC_{0\text{-}24h}$) 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/m^2), 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/m^2), 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 ≥ 65 years of age, while 15% were 75 years and over. No overall differences in effectiveness 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 ≥ 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 ≥ 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 ≥ 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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proposed by the working group with regard to existing entities already widely recognized. These concepts included the following:

- In clear cell RCC, multicystic clear cell RCC is best considered as a neoplasm of low malignant potential.
- Subtyping of papillary RCC is worthwhile and the oncocystic variant of papillary RCC should not be considered a distinct entity.
- The chromophobe RCC category has at least for now, gained another subtype. This is the hybrid oncocyte chromophobe tumor. This tumor occurs in 3 settings—Birt-Hogg-Dube Syndrome, renal oncocytosis and as a sporadic neoplasm.

Main Subtypes of RCC

Renal cancers encompass many distinctive subtypes of neoplasms that arise in the kidney parenchyma. The most common subtype is clear cell renal cell carcinoma (ccRCC) summing up ~75% (**Figure 1**) kidney cancers, and the remaining 25% are aggregates of rare kidney cancers and commonly referred to as non-clear cell RCC (nccRCC). Within nccRCC, papillary type I (pIRCC) is at 5-10%, papillary type II (pIIRCC) at 5%, chromophobe type (chRCC) at 5%, unclassified type (ucRCC) at 5%, TFE-fusion type (tfeRCC) at 1%, collecting duct type (cdRCC) at 1%, me-dullary type (mdRCC) at 1%, and several <1% morphologically distinct types. Each of these different types of kidney cancer can be characterized by different histologies, clinical courses, and responses to therapies, and are associated with alterations of different tumor suppressors and/or oncogenes. With the technical advance in next-generation sequencing, efforts led by kidney cancer TCGA (the cancer genome atlas) working groups (KIRC, clear cell; KICH, chromophobe; KIRP, papillary) have begun to provide a better genomics picture on major subtypes of RCC. However, those 1% rare subtypes are poorly studied. Furthermore, how many disease entities are currently aggregated under the "unclassified" subtype is unknown. The molecular determinants of individual RCC subtypes will be discussed in the second half of this two-part series.

Clinical Difficulties that nccRCC Patients and Their Physicians Encounter

Over the past decade, we kidney cancer clinicians have conducted multiple international phase III trials, leading to the approval of new effective drugs for metastatic clear cell type kidney cancer (ccRCC), including sunitinib, sorefenib, pazopanib, axitinib, bevacizumab, everolimus, and temsirolimus. Current treatment has greatly extended the life expectancy of metastatic ccRCC patients from 12-18 months to 30-36 months. Despite these marked strides against ccRCC, the remaining 25% of kidney cancer patients with so-called non-clear cell renal cell cancer (nccRCC) who develop metastasis are left with no standard of care option and now fare worse than ccRCC patients (**Figure 2**).[9]

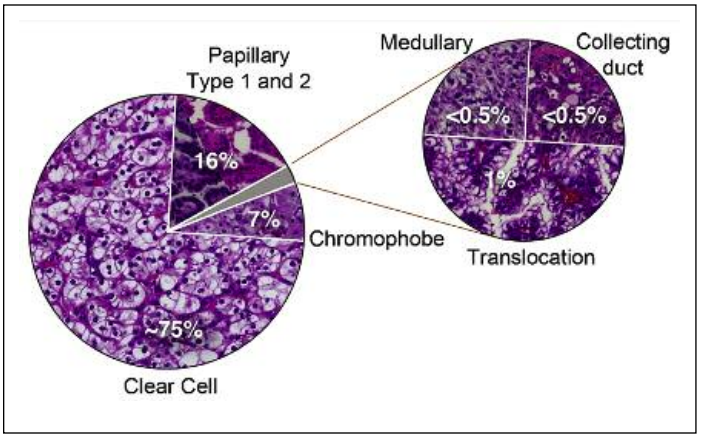

Figure 1. Pie chart showing distribution of the most common histologic subtypes of renal cell carcinoma. Medullary, collecting duct, and translocation renal tumors make up approximately 2% renal cell carcinomas.

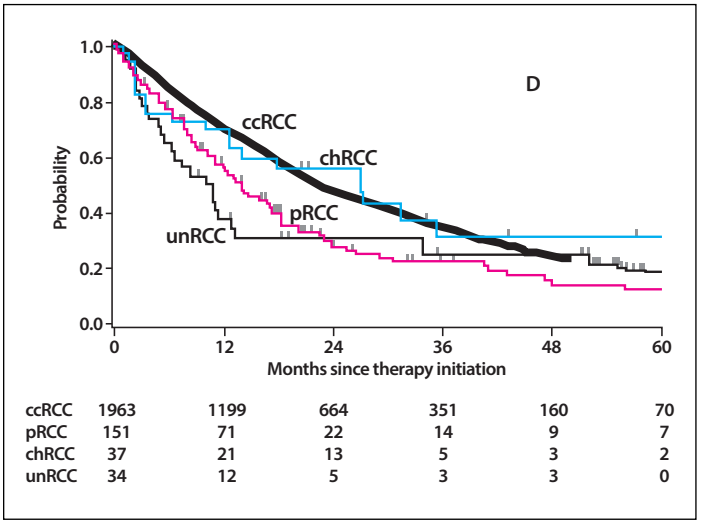

Figure 2. Probability of survival in different tumors shows worse prognosis in non-clear cell RCC.

Working Toward a Prognostic Model in Non-clear Cell RCC

One of the goals of efforts to further characterize variations of RCC is to propose models of different phenotypes that could be useful in treatment situations among patients whose disease has been relatively undifferentiated. A case in point is the subgroup with non-clear cell RCC. In these patients the goal of one international group was to reliably predict overall survival (OS) and time to treatment failure (TTF). For example, the 20% of kidney cancer patients with non-clear cell RCC served as a study population for the International mRCC Database Cosortium (IMDC)(13). The IMDC, or Heng model, has been a useful prognostic model in major clinical trials of targeted therapies.[14] In two reports on development of the Heng model, the criteria (essentially 6 independent predictors of poor survival) were validated without consideration of the histological subtypes.[11,12] Heng et al assumed that the results they obtained were largely affected by the clear-

(continued on page 101)

Dynamic New Initiatives in RCC Target Elusive Issues, Including Tumor Heterogeneity, Metabolic Derangements and Genomics

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Working in tandem with Robert Motzer, MD, Dr Hsieh is focused on building a translational kidney cancer program to decode the molecular basis underlying treatment response and cancer metastasis. The goal of this work is to develop personalized treatment regimens for patients with kidney cancer.

The concept of renal cell carcinoma (RCC) as a uniform malignant phenotype has been reengineered so many times that it bears no resemblance to later classification schemes. In some ways, even the WHO 2004 classification system is losing its relevance as well. Remarkable advances in the understanding of basic morphology, immunohistochemistry, cytogenetics, and molecular pathology have ushered in a new era of classification of RCC. And much more is on the horizon, as consensus conferences and study groups introduce new models of RCC subtypes that only recently have been integrated into our understanding of pathologic variants of the disease.

Whether we refer to them as "non clear cell" or "non-conventional" RCC, such tumors histologically are not as elusive as previously thought and new reports are revealing more of the characteristics that enable our identification of them as emerging entities. Over the last decade there have been refinements in many existing categories within the 2004 WHO classification system. More refinements are in the preliminary stages as research initiatives, such as those under study at the Memorial Sloan-Kettering Cancer Center, point toward new directions. Although the research initiatives are only now being launched, they serve as an important reminder of gaps in our knowledge base with regard to the understanding of:

- The mechanisms and therapeutics of anti-angiogenic resistant clear cell RCC.
- The need for an integrated molecular and imaging approach of kidney cancer as a metabolic disease.
- Tumor heterogeneity of kidney cancer and its impact on clinical/pathologic outcomes and treatment response.
- The genomics and therapeutics of rare kidney cancers.

The ideas and focus behind these initiatives are still in development at MSKCC, but their aims and objectives suggest the line of thinking to further characterize approaches to RCC.

One of the directions to be pursued is to investigate the mechanisms and therapeutics of anti-angiogenic resistant clear cell RCC. The goals of this proposed initiative are to:

(1) Discover biomarkers of response and resistance to anti-angiogenic TKI in human ccRCC tumors.
(2) Establish additional PDX models of ccRCC that recapitulate primary resistance to anti-angiogenic TKIs and molecularly dissect the underlying resistance mechanisms.
(3) Identify therapeutic strategies for ccRCC patients with primary resistance to anti-angiogenic TKIs.

A second initiative at MSKCC focuses on an integrated molecular and imaging approach of kidney cancer as a metabolic disease. Among the aims of researchers are the following objectives. To investigate the molecular basis of metabolic derangements in RCC, MSKCC investigators would:

(1) Perform multidimensional integrated genomics on distinct metabolic clusters of ccRCC.
(2) Determine the role of elevated 2-HG in ccRCC.
(3) Investigate metabolic pathways that associated tumor aggressiveness

Novel metabolic imaging of RCC would be utilized to:

(1) Characterize cancer metabolism utilizing a combination of isotope tracing Mass Spectroscopy (MS) and hyperpolarized Magnetic Resonance (MR) derived flux
(2) Image RCC mouse models using hyperpolarization (HP) MR imaging.
(3) Perform HP MR imaging on human kidney cancer patients.

One of the most timely areas to be addressed concerns tumor heterogeneity and treatment responses. The research initiatives in this regard will:

(1) Assess the impact of intratumoral heterogeneity (ITH) on clinical and pathologic outcomes across the disease spectrum of ccRCC and on the development of biopsy-based prognostic models.
(2) Study the effect of ITH on tumor immune microenvironment and its impact on therapeutic response.
(3) Investigate the spectrum of ITH and its implications in metastatic disease utilizing a Research Medical Donation (Rapid Autopsy) Program.

Still another area to be addressed covers the genomics and therapeutics of rare kidney cancers. The goals of an initiative on this topic will:

(1) Delineate the genomic landscape of aggressive renal cell carcinoma with unclassified histology to develop a molecular classification scheme.
(2) Dissect the molecular mechanism underlying a novel subset of unclassified RCC and develop genetically engineered mouse models for preclinical studies.
(3) Develop therapeutic strategies for unclassified RCC.

As these ideas coalesce and a protocol for investigative work takes shape, teams of researchers at MSKCC will report on their findings and their possible translational impact for clinical practice and future trials.

Original Research

Marriage Improves Outcomes for Patients With Renal Cell Carcinoma

Kelly K. Hollenbeak, RN BSN[1]

Madeline S. Hollenbeak, BS-C[2]

Christopher S. Hollenbeak, PhD[3]

Introduction

The incidence of renal cell carcinoma (RCC) is on the rise. Between 1975 and 1995, incidence rates per 100,000 person-years increased by 2.3%, 3.1%, 3.9%, and 4.3% annually for white men, white women, black men, and black women, respectively.[1] In 2010, approximately 58,000 people were diagnosed with RCC, and about 13,000 were expected to die from it in the United States.[2] Across the world, there were an estimated 270,000 cases and 116,000 deaths due to RCC in 2008.[3]

Many studies have observed that in cancers with high mortality rates, outcomes have been better in patients who are married as opposed to those who are single, widowed or divorced. Studies have suggested that the extended survival of married cancer patients may be attributable to emotional support provided by the spouse or by advocacy for aggressive treatment on the part of the spouse. This relationship effect has been studied in lung, breast, bladder, prostate, and colon cancer, but has not been studied in renal cell carcinoma.[4]

The purpose of this research was to study marriage and the outcomes of patients with RCC to determine whether those who are married have a greater survival rate as compared to those who are single, divorced, widowed, and separated. In addition, previous studies have shown that married men fare better than married women with cancer, presumable as a result of better nurturing. So the differential effect for men versus women was also evaluated to determine whether or not men who are married have better outcomes of survival than women who are married.

Table 1. Demographic and Disease Characteristics of Patients With Renal Cell Carcinoma

Variable	Married N=50,741	Unmarried N=28,614	*P*-Value
Age	60.9	62.4	<0.0001
Sex			<0.0001
Male	68.4%	50.0%	
Female	31.6%	50.0%	
Race			<0.0001
White	86.4%	79.4%	
Black	16.3%	24.2%	
Other	6.1%	4.7%	
Marital Status			
Single	0.0%	39.7%	
Married	100.0%	0.0%	
Separated	0.0%	3.1%	
Divorced	0.0%	25.8%	
Widowed	0.0%	31.4%	
Histology			<0.0001
Clear Cell	51.0%	46.6%	
Papillary	9.0%	8.7%	
Chromophobe	4.9%	4.1%	
NOS	32.9%	38.3%	
Stage			<0.0001
Local	67.1%	65.2%	
Regional	16.3%	14.8%	
Distant	16.6%	20.0%	

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Financial disclosure: All authors have nothing to disclose.

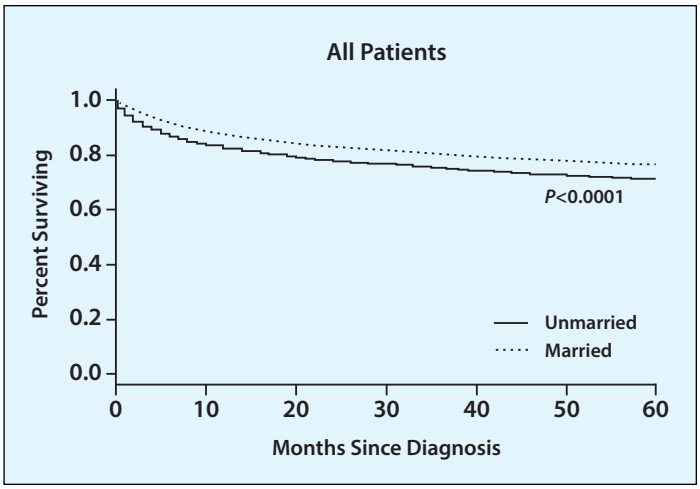

Figure 1: Survivor functions stratified by marital status.

Methods

Data used in this research were from the Surveillance, Epidemiology, and End Results (SEER) data set, a large national tumor registry maintained by the National Cancer Institute.[5] Starting with all cases of RCC diagnosed between 2000 and 20011 in seventeen SEER geographic areas, we excluded patients who had more than one form of cancer or who had a recurrence of their RCC. We also excluded patients with missing demographic data or whose marital status was unknown. Finally, we excluded all cases that had a histological class outside of the most common seen (clear cell, chromophobe, papillary, and RCC not otherwise specified (NOS). After applying these exclusions, a sample of 77,040 cases of RCC were available for analysis.

Variables extracted from the dataset included age, sex, race, marital status, stage of cancer, histology of cancer, treatment, death caused by cancer, and the number of months followed until death or final follow-up. Married was defined as currently married or partnered. Patients who were single, separated, divorced, or widowed were counted as unmarried. Stage was defined using SEER historic stage definitions of local, regional, and distant.[6] Local stage indicated the tumor was confined to the kidneys. Regional stage indicated the primary tumor extended beyond the kidneys to surrounding tissues. Distant stage indicates that the cancer has metastasized to other parts of the body.

The statistical analysis was used to determine whether married patients had a significantly longer survival than unmarried patients, controlling for other important patient and disease characteristics. Characteristics of married patients were compared to characteristics of unmarried patients using *t* tests for continuous variables and chi-square tests for binary and categorical variables. Survivor functions were estimated using the Kaplan Meier method with comparisons made between strata using the log rank test.[7] Multivariate analysis of survival was performed using a Cox proportional hazards model.[8] Results were presented as hazard ratios. All analyses were performed using Stata (version 12, College Station, TX) and R (version 3.1, www.r-project.org) software.

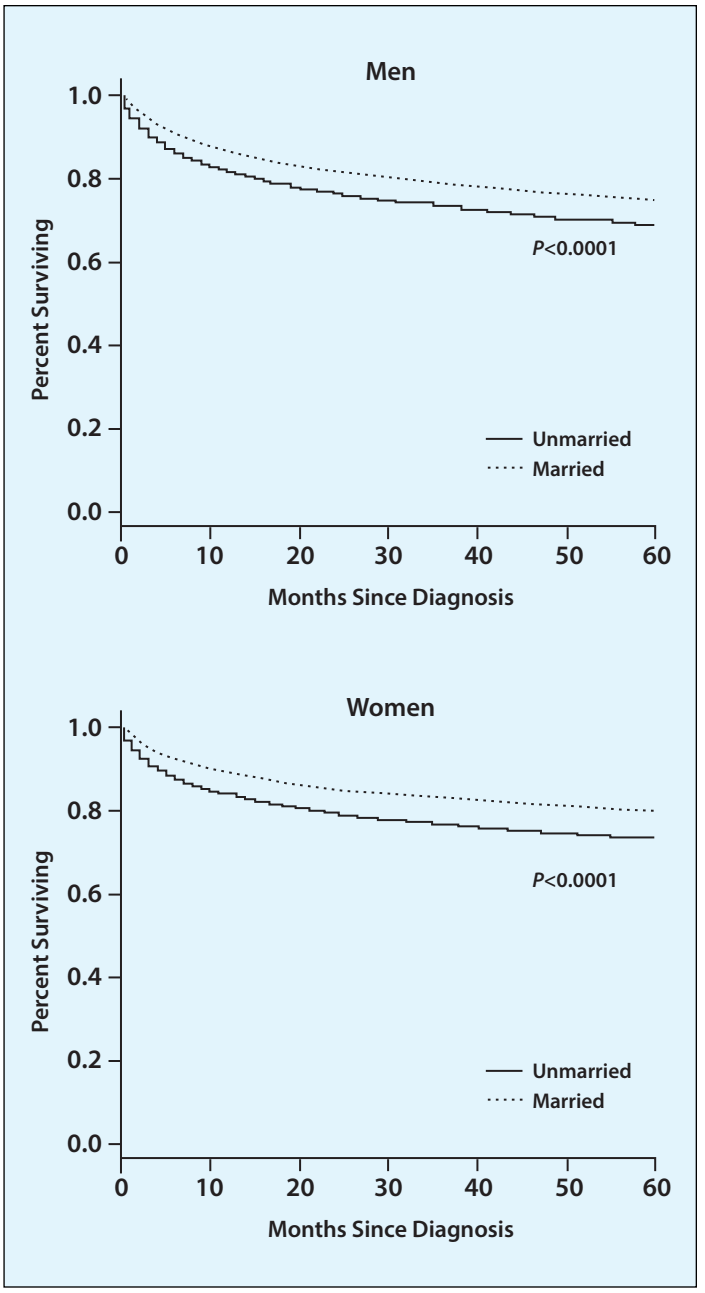

Figure 2: Survivor functions stratified by sex and marital status.

Results

As seen in **Table 1**, 63.9% of RCC patients were married and 36.1% were unmarried. Married patients with RCC were similar to unmarried patients with RCC in terms of age, histology, and stage of cancer progression. The stage of cancer was also similar between married and unmarried patients, with most disease being localized (67.1 vs. 65.2%), followed by regional (16.3 vs. 14.8%) and distant (16.6 vs. 20.0%). There were also some important differences between married and unmarried patients. While 31.6% of married RCC patients were women, 50.0% of unmarried patients were women. There were also more

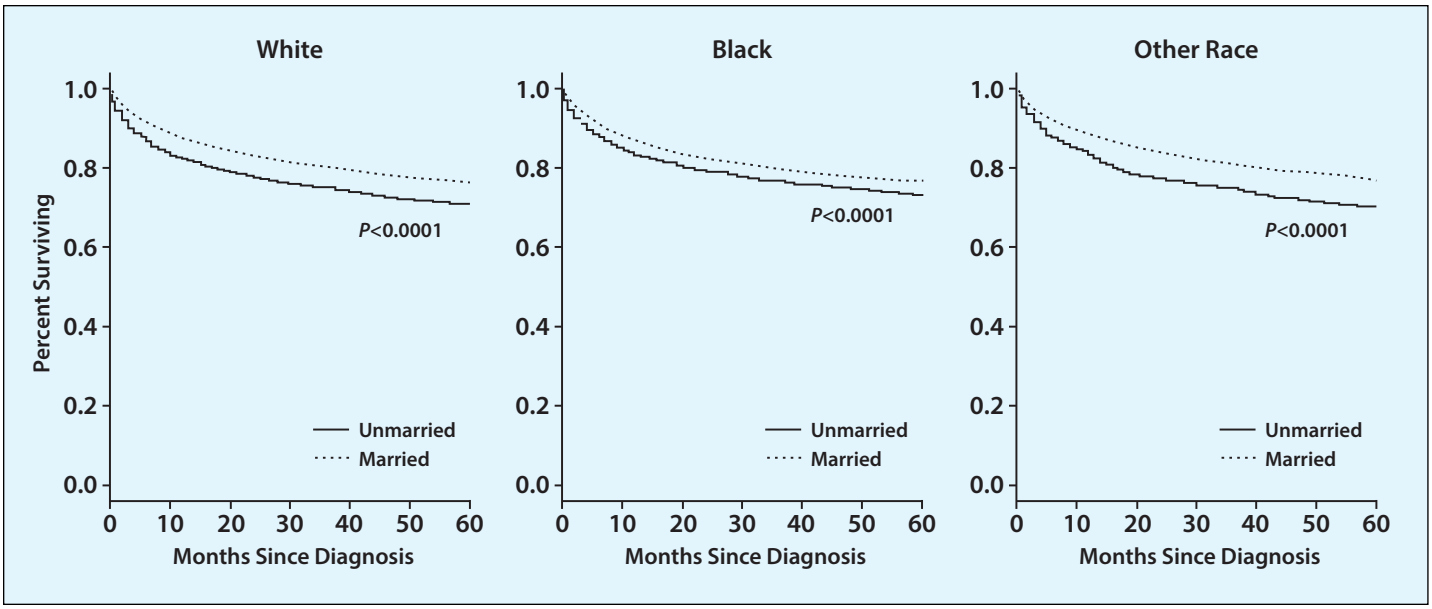

Figure 3: Survivor functions stratified by race and marital status.

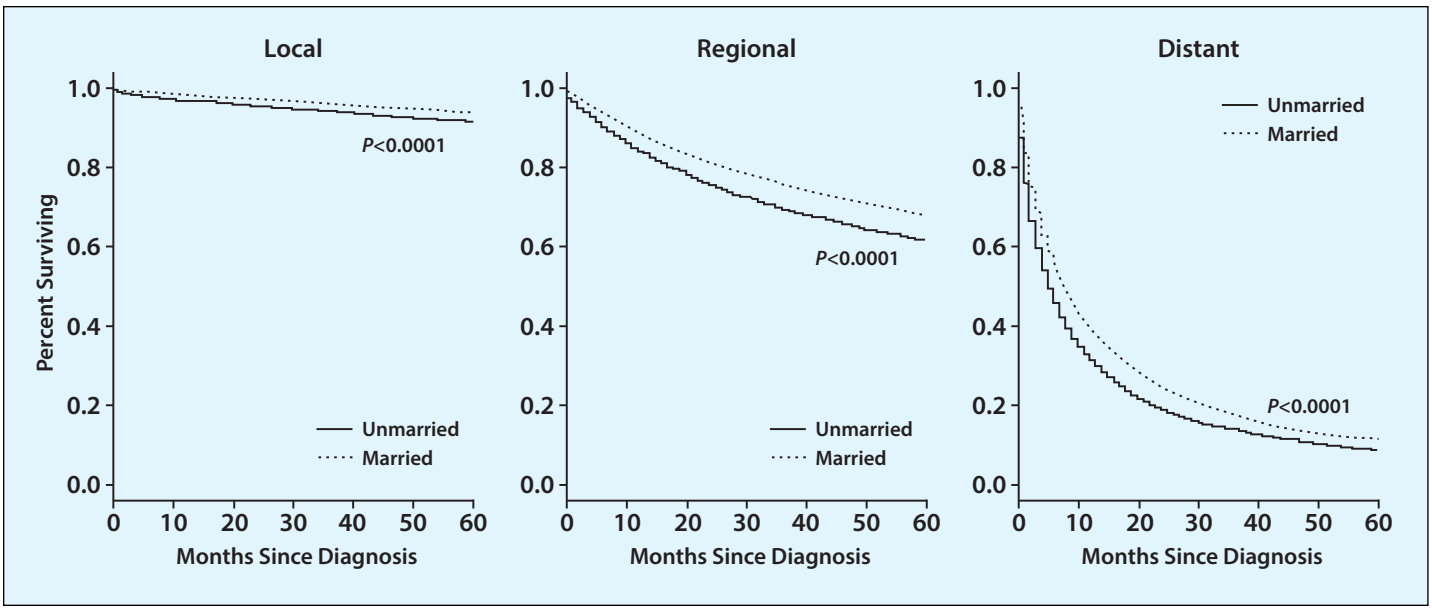

Figure 4: Survivor functions stratified by stage of disease and marital status.

than twice as many unmarried, black patients (24.2%), as there were married, black patients (16.3%).

A clear survival advantage for married patients is seen in in **Figure 1**, which shows that the one-year survival rate for married patients was 88.7%, compared to 85.0% for unmarried RCC patients. This benefit extended through five years of survival, with married RCC patients surviving at a rate of 77.5%, and the unmarried patients surviving at an average rate of 73.5% (p<0.0001).

We explored, in **Figure 2**, whether the marriage benefit was observed in both men and women. Women who were married had a 90.4% survival rate at one year; unmarried women were lower at an 86.2% survival rate (p<0.0001). This marriage benefit lasted through five years. At five years, married women had an 81.0% survival rate while unmarried women had a 75.7% survival rate (p<0.0001). One year after diagnosis, 87.9% of married men had survived while 83.9% of unmarried men had survived. Five years following diagnosis, married and unmarried men had survival rate of 75.9% and 71.2%, respectively (p<0.0001).

We also sought to determine whether the marriage advantage was also observed across race groups (**Figure 3**). Among white patients, those who were married had an 88.7% survival rate one year after diagnosis while those who were unmarried had an 84.9% survival rate. Higher survival rates in married, white patients were also seen after five years, being 77.5% while unmarried, white patients had a survival rate of 73.2% (p<0.0001). Patients who were black had a similar survival benefit. After one

Table 2. Result of Multivariate Survival Analysis Using Cox Proportional Hazards Model.

Variable	Hazard Ratio	95% Confidence *Lower*	95% Confidence *Upper*	*P*-Value
Age				
20-40	REFERENCE			
41-60	1.34	1.21	1.48	<0.0001
61-80	1.70	1.54	1.88	<0.0001
80+	2.59	2.33	2.88	<0.0001
Sex				
Male	REFERENCE			
Female	0.93	0.90	0.97	<0.0001
Marital Status				
Married	0.86	0.83	0.89	<0.0001
Unmarried	REFERENCE			
Race				
White	REFERENCE			
Black	1.05	1.01	1.09	0.018
Other	0.90	0.84	0.96	0.002
Histology				
Clear Cell	0.01	0.56	0.59	<0.0001
Papillary	0.02	0.55	0.65	<0.0001
Chromophobe	0.02	0.25	0.35	<0.0001
NOS	REFERENCE			
Stage				
Local	REFERENCE			
Regional	5.62	5.35	5.90	<0.0001
Distant	31.07	29.74	32.46	<0.0001

year, married, black patients had an 88.3% survival rate, while those who were unmarried had an 85.7% survival rate. After five years, among patients who were black, married and unmarried patients had 78.1% and 75.4% survival rates, respectively (p<0.0001). For patients of all other races, those who were married continued the trend of having higher survival rates.

We also studied survival rates of married and unmarried RCC patients by stage of disease. In every stage (local, regional, or distant), and at one year and five years, the married patients' survival times exceeded that of the unmarried patients (**Figure 4**).

0We performed a multivariate survival analysis using a Cox proportional hazards model to test whether married patients had better survival after controlling for patient- and disease-specific characteristics. As seen in **Table 2**, after controlling for other factors, married patients had a hazard ratio of 0.86 (p<0.0001), suggesting a significant survival advantage was associated with marriage after controlling for other factors.

Discussion

In this study of the relationship between marital status and survival for patients with RCC, we found an increased survival rate among married RCC patients compared to patients who were single, widowed or divorced. These results held across stratifications of sex, race, and stage. There was a difference in one-year survival of more than ten percentage points between married women (83.1%) and unmarried men (72.3 %). The same comparison showed an even wider difference after five years, with a survival difference of 13% percentage points between married women (69.6%) and unmarried men (55.8%) with RCC.

We also found that among married patients, women had a higher rate of survival at one and five years, suggesting a gender effect as well as a marriage effect. This marriage and gender effect held across all stages of disease. This was not an expected finding, considering that results in other marriage and outcomes in cancer studies showed men to have higher survival than women. Additionally, Umberson (1992) argued that women are more likely than men to attempt to control the health of others, and thereby provide more health care to a male spouse, yielding a higher survival rate for the male cancer patients.[9]

There are strong reasons to suspect that marriage could improve outcomes for patients with cancer. Previous studies have shown that married patients were more likely to be diagnosed at an earlier stage and to receive more aggressive treatment.[10,11] Another reason we might expect married patients to have better outcomes than unmarried patients is that they may have a better social and emotional support system. Krongrad et al. evaluated the association between marital status and survival in patients with prostate cancer, focusing specifically on social support and/or mood. In his research, social support directly affected immune function.[12] For the married patients, the immunologic effect was positive. Similar social support effects were found in studies of older women with bladder cancer.[4] Kravdal (2001) studied twelve different types of cancer with favorable results for married cancer patients.[13]

Another reason we may expect married RCC patients to have better outcomes is that if the spouse is working, the household may have better financial resources, which can lead to better health behaviors and more aggressive treatments. The lung cancer group at the Mayo Clinic assessed the impact marriage had on the quality of life in patients with non-small cell lung cancer.[14] They found that marriage appeared to confer benefits to patients in terms of both social support and economic advantages. Having better financial resources allowed the married cancer patient access to health care and more aggressive therapy. Work by Osborne et al. (2005) on the influence of marital status on breast cancer showed that the effect of marital status on survival was stronger among those females who were financially more advantaged.[15] Higher income was also associated with healthier behaviors, such as regular doctors visits and screening exams. This led to early detection in breast cancer patients.[9]

The results of this study suggested better outcomes for

married RCC patients, yet there were limitations to this study. The data set was observational so there is the possibility that there were unmeasured variables that were correlated with both marriage and outcomes that account for the marriage benefit. Also, the secondary hypothesis that suggests a nurturing effect and a gender effect was difficult to test. In this research, the hypothesis was not supported. Married females actually had better outcomes than other strata. Thus, a nurturing effect, if it existed, could have been overwhelmed by a gender effect. Even in the unmarried stratum, unmarried women had a higher survival rate than unmarried men. We were unable to determine whether nurturing played a role.

Studies have shown that there are higher incidence rates of RCC in males. This could be one of the factors that might have resulted in better outcomes in women and not the nurturing effect. Another study supports this higher rate among men, suggesting that protein kinase C marker accounts for the higher rate of disease among men.[16]

Another limitation relates to the categories of unmarried patients. While a large proportion of unmarried patients were widowed, separated, and divorced, it is not known how long ago their marital status changed. Some of the patients may have become widowed or divorced, or even married just prior to their diagnosis. This change in status could have had an impact on the patients.

0As for this study, we were able to analyze the marriage effect and outcomes for renal cell carcinoma. The results from the data demonstrated that marriage has a positive effect on the survival rate for patients with RCC at one and five years. This marriage benefit coincides with the previous research performed on outcomes for lung, breast, bladder, prostate, and colon cancer. The gender effect found in this research showed that women outlived the men, and married women survived the longest. This was contrary to the nurture effect that was anticipated in our hypothesis. The question still remains as to the reason women have had better rates of survival, and therefore, deserves further exploration in future studies.

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EDITOR'S MEMO *(continued from page 74)*

there include some state-of-the-art plans to investigate the molecular basis of metabolic derangements in RCC, all of which will take us light years away from the vanishing era when RCC was viewed as a uniform malignant phenotype. This is an exciting time for the reclassification of RCC tumors and the old schemes, such as the WHO criteria from 2004 need to be retooled and reconfigured to reflect the importance of new findings and the broader spectrum of tumor heterogeneity.

Robert Figlin, MD
Editor-in-Chief

Reference: Shuch B et al. Understanding pathologic variants of renal cell carcinoma: distilling therapeutic opportunities from biologic complexity. *Eur Urol*. 2014; http://dx.doi.org/10.1016/j.eururo.2014.04.029.

We're enrolling to the ADAPT Study, providing you and your patients with a fully personalized option to treat their metastatic Renal Cell Carcinoma.

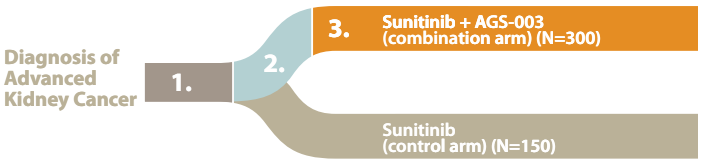
The ADAPT (**A**utologous **D**endritic Cell Immunotherapy (**A**GS-003) **P**lus Standard **T**reatment) Phase 3 study is currently investigating the combination of an autologous dendritic cell based immunotherapy, AGS-003, plus standard targeted drug therapy (initiating with, but not limited to, sunitinib). The study will compare the following outcomes between study arms: 1) Overall survival (primary endpoint), 2) PFS, response rate and safety (secondary endpoints) and 3) immunologic response (exploratory).

Patients with newly-diagnosed, synchronous metastatic RCC at presentation must meet the following key eligibility criteria:

- ≥ 18 years of age
- Newly diagnosed with metastatic RCC and no known brain metastases
- Good candidate for standard surgery (partial or cytoreductive nephrectomy)
- Good candidate to receive standard targeted drug therapy (initiating with Sunitinib)
- No autoimmune disorders (eg. RA, MS, SLE)

To learn more, please visit the ADAPT study website at www.adaptkidneycancer.com or contact the study team at clinicalteam@adapt-study.com

ADAPT Study:



1. Surgery

(Tumor sample taken)

2. Blood Donation

(Only for patients who are assigned to the AGS-003 treatment regimen)

3. Standard Treatment with Sunitinib + AGS-003

(Begins 6-weeks after 1st dose of sunitinib)

Argos THERAPEUTICS

Recapping the Results From ASCO 2014: Exciting Data but Wrapped in a Cautionary Tale

Sumanta Kumar Pal, MD
Assistant Professor
Department of Medical Oncology
& Therapeutics Research
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City of Hope
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Stu Chapman
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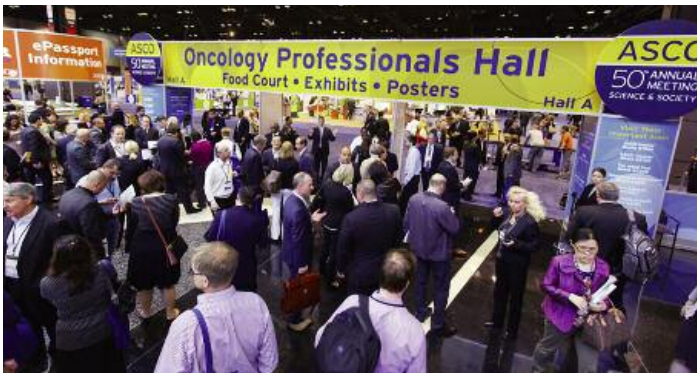

Attendees flocked to the Exhibit Hall at 2014 ASCO meeting to consult and view presentations.

Each annual meeting of the American Society of Clinical Oncology (ASCO) tends to run true to form in renal cell carcinoma (RCC): there is an initial burst of excitement following announcement of new results and promising signs of breakthroughs in therapy or at least another incremental step toward them. But then, a cautionary tale begins to emerge as the data undergo closer scrutiny and the take-home messages are viewed perhaps more critically.

This year's meeting of ASCO provided much the same scenario. There were exciting trends to cheer—use of the immune check point inhibitors (CTLA-4, PD-1, and PD-L1), the ESPN data looking at either sunitinib vs everolimus in non-clear cell renal cell carcinoma , and possibly improved survival benefit associated with use of high-dose interleukin-2 (IL-2). In each case, however, the need for confirmation in large trials is still evident, particularly with respect to the immunotherapy results and attention focused on the potential use of PD-1 inhibitors.

Immunotherapy: Checkpoint Inhibition Gathers Momentum

Immunotherapy was the big story to emerge from the 2014 sessions, as it was the previous year, and there is little doubt that the findings from the phase 1 trial of nivolumab will continue as one of the leading trends in the months ahead as this agent is evaluated in a phase 3 trial. Combining nivolumab and ipilimumab, a fully human monoclonal antibody to CTLA-4, has shown encouraging clinical activity and acceptable safety in advanced melanoma and these results serve as the basis for evaluating the combination in mRCC. In the report by Hammers et al (Abstract 4504) patients with mRCC were randomized to receive nivolumab 3 mg/kg + ipilimumab 1 mg/kg (arm N3 + I1) or nivolumab 1 mg/kg + ipilimumab 3 mg/kg (arm N1 + I3) IV Q3W for 4 doses, then nivolumab 3 mg/kg IV Q2W until progression/toxicity. The primary objective was to assess safety/tolerability; secondary objective was to as- sess antitumor activity.

Patients were randomized to N3 + I1 (n=21) and N1 + I3 (n=23). Most patients (n=34; 77%) had prior systemic therapy (N3 + I1: 16; N1 + I3: 18). Treatment-related adverse events (AEs) were seen in 39/44 pts (89%); 7 patients (16%; N3 + I1: 2; N1 + I3: 5) discontinued due to any-grade related AEs. Grade 3–4 related AEs occurred in 19 patients (43%; N3 + I1: 5; N1 + I3: 14), most commonly elevated lipase (16%, n=7), elevated ALT (11%, n=5), diarrhea (9%, n=4), colitis (5%, n=2), elevated amylase (5%, n=2). No grade 3–4 pneumonitis was seen. Objective response rate (ORR) was 29% (N3 + I1) and 39% (N1 + I3). Duration of response (DOR) was 4.1+ to 22.1+ weeks (all 6 responses ongoing) in N3 + I1, and 6.1+ to 18.3+ weeks (8/9 responses ongoing) in N1 + I3. Responses occurred by first tumor assessment (week 6) in 67% of responding patients in both N3 + I1 and N1 + I3. Stable disease (SD) was seen in 7 (33%) (N3 + I1) and 9 (39%) (N1 + I3).
Conclusion: Nivolumab plus ipilimumab showed acceptable safety and encouraging antitumor activity in mRCC, with most responses ongoing. Follow-up, expansion cohorts at these doses and an additional dose cohort (nivolumab 3 mg/kg plus ipilimumab 3 mg/kg) are being assessed in a phase 3 trial.

The extent to which nivolumab can ultimately change

the landscape of treatment in RCC awaits results from phase 3 trials. After the ASCO meeting, the first PD-1 inhibitor was approved for use in melanoma. Although this approval is expected to generate some limited off-label use for RCC, the conventional wisdom among key opinion leaders in RCC is that the agent needs to be evaluated in phase 3 trials with definitive results before recommendations can be made on its use in RCC.

In another presentation involving nivolumab, Motzer et al discussed results in a phase 2 trial of monotherapy with this checkpoint inhibitor (Abstract 5009). The response rates were slightly lower than what has been reported earlier. PFS was also slightly lower. The monotherapy trial now moves on to a phase 3 study to further assess the efficacy of nivolumab. Patients with clear-cell mRCC (≥1 agent targeting VEGF pathway; ≤3 prior systemic therapies) were randomized (blinded 1:1:1) to nivolumab 0.3, 2 or 10 mg/kg IV Q3W until progression or toxicity. The primary objective was to evaluate the dose-response relationship measured by progression-free survival (PFS). Secondary objectives included overall survival (OS), objective response rate (ORR) and safety assessment.

All 168 patients received prior systemic therapy (70% received ≥2) including VEGFR TKIs (98%), mTOR inhibitors (38%) and immunotherapy (24%). 25% were MSKCC poor risk. All had >16 months of follow-up. No dose-response relationship was noted for PFS. PFS and ORR were similar across doses (Table). For 0.3 mg/kg, median duration of response was 15.7 months and median OS was 18.2 months; for other doses medians were not reached. Across doses 19/35 responders (54%) had objective responses lasting >12–20+ months. Rates of grade 3–4 related adverse events (AEs) were ≤17% for all doses (Table). There was no grade 3–4 pneumonitis. For 0.3, 2 and 10 mg/kg, 1 (2%), 6 (11%) and 4 (7%) patients, respectively, had treatment-related AEs that led to discontinuation.

Conclusion: Antitumor activity was observed with nivolumab in this pretreated mRCC population including objective responses of long duration. No dose-response relationship for PFS was noted and the safety profile was acceptable. Median OS was 18.2 months for the 0.3 mg/kg dose and was not reached for 2 or 10 mg/kg.

	0.3 mg/kg n=60a	2 mg/kg n=54	10 mg/kg n=54
Median PFS, months (80% CI)	2.7 (1.9, 3.0)	4.0 (2.8, 4.2)	4.2 (2.8, 5.5)
ORR, n (%)	12 (20)	12 (22)	11 (20)
Median OS, months (80% CI)	18.2 (16.7, NR)	NR	NR
Treatment-related AE, n (%)			
Grade 3–4	44 (75) 3 (5)	36 (67) 9 (17)	42 (78) 7 (13)

[a]Safety analysis included 59 treated pts; CI=confidence interval; NR=not reached.

The ESPN Trial: Sunitinib Favored in Non-clear Cell RCC but With Caution

Temsirolimus was previously shown to produce overall survival (OS) benefit in poor-risk RCC including nccRCC. The ESPN randomized phase 2 trial presented by Nizar et al (Abstract 4505) compared everolimus with sunitinib in a crossover design in metastatic nccRCC. Primary endpoint was PFS in first-line (1L). Secondary endpoints were PFS in second-line (2L), safety, and OS.

Seventy-three patients were enrolled; 68 were eligible and evaluable (median age 59, 43 males [63%], 52 pts [77%] had prior nephrectomy). Twenty-seven patients had papillary, 11 had chromophobe, 9 had unclassified, 7 had translocation, 13 had sarcomatoid, and 1 had oncocytic RCC. Thirty-five patients received everolimus (good-risk 4, intermediate-risk 29, poor-risk 2); 33 patients received S (good-risk 4, intermediate-risk 29). ORR with sunitinib in 1L was 12% (2 patients had chromophobe, 1 had papillary type 1 and 1 had 99% sarcomatoid); ORR with everolimus in 1L was 0%. Median PFS in 1L with sunitinib was 6.1 months (95% CI: 4.7, 10.8) and 4.1 months with everolimus (95% CI: 2.7, 7.4); p = 0.25.

Thirty-eight patients received 2L therapy (S 19, E 19). Median PFS in 2L with sunitinib was 1.8 months and 4.3 months with everolimus. A total of 27 patients have died (8 had sunitinib and 19 had everolimus). Median OS with everolimus in 1L was 10.5 months; median OS with sunitinib in 1L was not reached; p=0.01. Toxicity was consistent with previous reports of both agents.

Conclusion: Based on futility analysis for PFS and inferior OS with everolimus compared to sunitinib in 1L, the Data and Safety Monitoring Board recommended termination of further patient accrual on this trial. Everolimus cannot be recommended as 1L option in nccRCC.

This was an ambitious study, and the authors are to be commended for conducting a study in the setting of these rare histologies. These results need to be further interpreted with caution because the subsets in nccRCC were small. One of the limitations of the study is that it grouped these subsets under one umbrella and one protocol. Further study is needed in a trial with specific, biologically driven subgroups of nccRCC and a protocol that looks at papillary, chromophobe, and other subtypes individually.

Interleukin 2, AG-003: Promising Extensions of Survival

One of the key questions looming for a future ASCO meeting is to what extent PD-1 inhibition may obviate the need for the use of high-dose IL-2. It is too early to speculate on this issue, but data presented at ASCO 2014 from current Registry Data (2007-2012) indicate a major survival benefit for all IL-2 treated patients (n=97) with the median not reached for those with stable disease, partial response or complete response, and a median of 40 months for those with progressive disease according to Morse et al. (Abstract 4523).

Conclusion: The PROCLAIM registry documents a vastly improved OS for HD IL-2 compared to historical results

during a time interval marked by the advent of targeted therapy for advanced RCC.

A continuing focus involving immunotherapy involves the use of the vaccine AGS-003. In a small phase 2 study (n=21, 10 poor risk, 11 intermediate risk), long-term survival data from the combination of autologous immunotherapy (AGS-003) plus sunitinib also showed promising extension of survival compared with historical controls treated with sunitinib alone, with a median overall survival ≥ 30 months, and 33% surviving for at least 54 months (Abstract 4524). Thus durable survival is the hallmark of treatment with immunotherapy for renal cell cancer and the benchmark for new therapies that are in development. This clearly surpasses targeted therapy, but the current goal should be to extend this to greater numbers of patients.

Conclusion: When compared to historical estimates of PFS and OS for unfavorable risk patients (time from diagnosis to treatment of less than one year), the addition of AGS-003 to sunitinib resulted in a 50% increase in median PFS, doubling of expected median OS, more than 50% of patients surviving long-term (OS ≥ 30 months) and 33% of patients surviving for at least 54 months. Currently the combination of AGS-003 plus sunitinib is being compared to sunitinib alone in a large phase 3 study (ADAPT). KCJ

(continued from page 90)

cell RCC subtype because it was the predominant histological subtype in the development and validation cohort. The key question left unanswered by these earlier reports, however, is whether the IMDC prognostic model can be applied in the non-clear cell subtype. Another question addressed by the IMDC was whether outcomes tended to be worse among the nccRCC group.

Kroeger et al[9] and the Consortium determined whether the IMDC prognostic model could be applied to survival outcomes of patients with nccRCC treated with first-line VEGF and mTOR inhibitors. By assessing the applicability to this subtype, Kroeger et al could differentiate responses to such therapy in nccRCC vs the ccRCC cohort in the study. Tumors with nccRCC histology included papillary RCC (n=5151, 59.9%), chromophobe RCC (n=537, 14.7%), collecting duct RCC (n=57, 2.8%), unclassified RCC (n=534, 13.5%), and RCC with Xp11 translocation (n=54,1.6%).The 6 independent predictors of poor survival evaluated included:

(1) Karnofsky performance status <80%.
(2) Time from diagnosis to treatment interval <1 year.
(3) Anemia
(4) Hypercalcemia
(5) Neutrophilia
(6) Thrombocytosis

The two conclusions emerging from this report, based on data gathered from 2215 patients with ccRCC and 252 with nccRCC, were (1) the risk model based on independent predictors of poor survival was reliable as a prognostic tool in the nccRCC group; and (2) even in the era of targeted therapy, the majority of nccRCC patients still had inferior clinical outcomes compared with patients with ccRCC. OS (12.8 vs 22.3 months) and TTF (4.2 vs 7.8 months) were worse in the nccRCC group compared to the ccRCC cohort. The prognostic model reliably discriminated 3 risk groups in the nccRCC patients: favorable, intermediate, and poor prognosis. The OS of these groups was 31.4, 16.1, and 5.1 months in these risk groups and TTF was 9.6, 4.9, and 2.1 months. Kroeger et al[9] suggest that the prognostic model could be useful in counseling patients and in clinical trial design. According to the authors, there is no other prognostic model that has been assessed exclusively in advanced nccRCC.

The prognostic model from the IMDC is important because it reflects similar efforts to further characterize not only nccRCC but other non-conventional RCCs. As Voss et al (17) point out, despite recent advances in the treatment of metastatic ccRCC, the optimal therapy for patients with advanced RCC with less common histologies has not been established. Most pivotal trials with targeted agents have exclusively enrolled patients with clear-cell histology, one exception being the Advanced Renal Cell Carcinoma (ARCC) trial demonstrating benefits of temsirolimus in patients with non-clear histology. Yet this study did not provide insight into the distinct nccRCC subtypes. This is why the report by Voss et al is of interest: it retrospectively analyzed outcomes of patients with nccRCC and sarcomatoid clear-cell and non-clear cell subtypes previously treated with mTOR inhibitors at Memorial Sloan-Kettering Cancer center. The aim was to explore the efficacy of these agents across various RCC variants.

The results were somewhat disappointing and Voss et al reached the following conclusions:

- Patients with metastatic ncRCC and sarcomatoid ccRCC can benefit from mTOR-targeted therapy, but the majority of patients respond poorly with these agents.
- Therapeutic effect varies greatly between individual patients, even within the same subgroups of disease.
- Importantly, objective responses or prolonged disease stabilization can be seen fora subset of patients across several of these rare cancers without clear association with any particular histologic phenotype.

Perhaps the message emerging from this report is that we can only speculate at this point as to why there is this variability in response to treatment exists. Voss et al postulate that differences in underlying tumor genetics, rather than the histopathologic phenotype alone, may be the explanation. In any case, the findings highlight the need for identification of predictive tissue biomarkers as part of a wider focus on more clearly characterizing these tumors of non-clear histology.

With the reexamination of the 2004 WHO classification scheme and more focused initiatives on identifying histologic variables as an important prognostic factor of survival, cytogenetic and molecular research has explored new pathological subtypes not previously recognized and that are part of what has been called cancer-specific or "localized non-conventional RCC (NCRCC)." These subtypes include Xp11.2t; renal medullary carcinoma, and RCC with neuroblastoma and MTSC RCC. A Korean retrospective study[14] compared clinical outcomes to determine independent prognostic factors according to histology in these non-conventional subtypes.

A total of 374 cases were examined, including 126 papillary (33.7%), 164 chromophobe (43.9%), eight collecting duct (2.1%), 40 unclassified (10.7%), 16 Xp11.2t (4.3%), seven mucinous tubular and spindle cell (1.8%) renal cell carcinomas and 13 oncocytomas(3.5%). During a mean follow up of 56.4 months, mean tumor size was 4.9 cm. The 4-year recurrence-free survival, overall survival and cancer-specific survival were inversely related to the increase of pathological T stages ($P < 0.001$). For histological type other than 13 oncocytomas and seven mucinous tubular and spindle cell renal cell carcinomas, the chromophobe showed the best prognosis of survival, followed by papillary, Xp11.2t, unclassified and collecting duct renal cell carcinomas, in this order. All survival rates were significantly different, as according to the histology ($P = 0.009$). The significant prognostic factors were preoperative body mass index (hazard ratio 0.76), serum albumin (hazard ratio 0.64), T stage (hazard ratio 2.28), the

sarcomatoid differentiation (hazard ratio 33.45) and lymphovascular invasion (hazard ratio 12.40) in pathology ($P < 0.05$).

The Korean study is significant as it helps clinicians to understand the comparative clinical course of different postoperative prognoses for each subtype of NCRCC, and to prepare for a better adjuvant management according to respective histology and prognostic factors. Not many studies have focused on subtypes of NCRCC with comparable numbers of patients with NCRCC over a long period of time like those of this study. Additionally, as molecular and cytogenetic biology have recently been spotlighted to identify the characteristics of RCC at gene and molecular levels, studies such as this one could have an important role. They may facilitate development of further management plans such as neo- or adjuvant targeted therapy for NCRCC patients; and this study could help to plan further analyses of molecular or cytogenetic biology on NCRCC as one of the differential references of different histologies from NCRCC, reflecting their clinically different prognosis .[15]

Conclusion

A dramatic change in the classification schemes for kidney cancer in the last two decades has important implications for determining prognosis and identifying therapeutic opportunities. As these new pathologic variants have been recognized, the traditional schemes used to characterize the disease are being replaced. With modifications and recommendations from groups analyzing these subtypes, an improved understanding of tumor heterogeneity will help guide clinical decision making.

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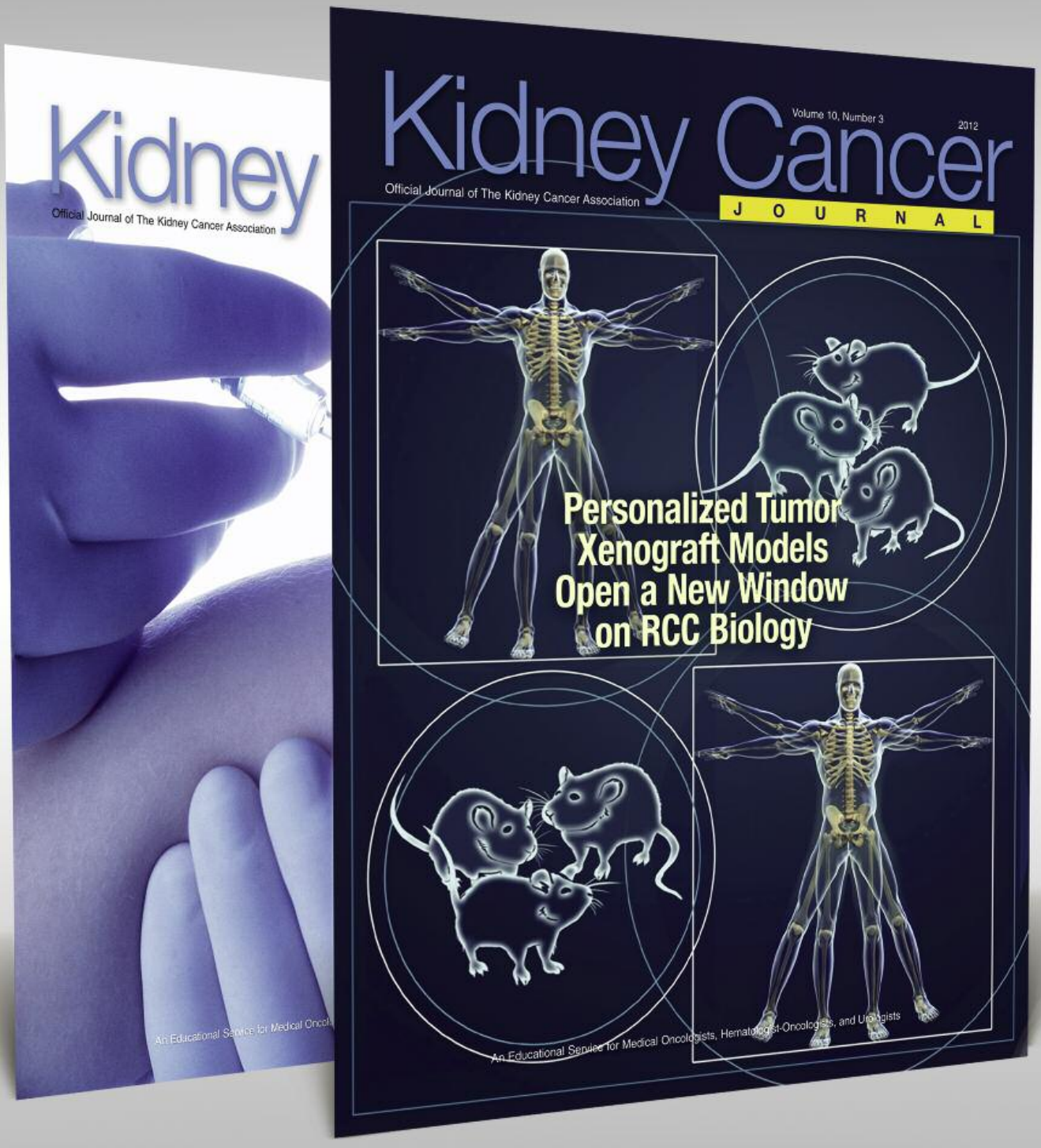

tients with non-ccRCC. PD-L1 expression was evaluated by immunohistochemistry in both tumor cell membrane and tumor infiltrating mononuclear cells (TIMC). PD-L1 tumor positivity was defined as ≥5% tumor cell membrane staining. For PD-L1 expression in TIMC, a combined score based on the extent of infiltrate and percentage of positive cells was used. Baseline clinico-pathological characteristics and outcome data [time to recurrence (TTR) and survival (OS) were correlated with PD-L1 staining. Among 101 patients, 11 (10.9%) were considered PD-L1+ in tumor cells: 2/36 (5.6%) of chromophobe RCC, 5/50 (10%) of papillary RCC, 3/10 (30%) of Xp11.2 translocation RCC and 1/5 (20%) of collecting duct carcinoma. PD-L1 positivity (PD-L1+) in tumor cells was significantly associated with higher stage and grade, as well as shorter OS. On the other hand, PD-L1 positivity by TIMC was observed in 57 (56.4%) patients: 13/36 (36.1%) of chromophobe RCC, 30/50 (60%) of papillary RCC, 9/10 (90%) of Xp11.2 translocation RCC and 5/5 (100%) of collecting duct carcinoma. A trend towards shorter OS was observed in patients with PD-L1+ in TIMC. PD-L1+ in both tumor cell membrane and TIMC cells were associated with shorter TTR.
Conclusion: In non-ccRCC, patients with PD-L1+ tumors appear to have worse clinical outcomes, although only PD-L1 positivity in tumor cells is associated with higher tumor stage and grade.

The somatic genomic landscape of chromophobe renal cell carcinoma. Davis CF, Ricketts CJ, Wang M, et al. *Cancer Cell*. 2014;26:319-330.
Summary: This study described the landscape of somatic genomic alterations of 66 chromophobe renal cell carcinomas (ChRCCs) on the basis of multidimensional and comprehensive characterization, including mtDNA and whole-genome sequencing.
Conclusion: ChRCC originates from the distal nephron compared with other kidney cancers with more proximal origins. Combined mtDNA and gene expression analysis implicates changes in mitochondrial function as a component of the disease biology, while suggesting alternative roles for mtDNA mutations in cancers relying on oxidative phosphorylation. Genomic rearrangements lead to recurrent structural breakpoints within TERT promoter region, which correlates with highly elevated TERT expression and manifestation of kataegis, representing a mechanism of TERT upregulation in cancer distinct from previously observed amplifications and point mutations. *[Editor's note: TERT (telomerase reverse transcriptase) is a protein-coding gene.]*

The association between metformin use and oncologic outcomes among surgically treated diabetic patients with localized renal cell carcinoma. Psutka SP, Boorjian Sa, Lohse CM, et al. *Urol Oncol*. 2014;Aug 18 [Epub ahead of print].
Summary: Metformin inhibits renal cell carcinoma (RCC) cell proliferation both in vitro and in vivo; however, clinical data regarding the effect of metformin in patients with RCC are lacking. This study evaluated the association of metformin use with outcomes among patients with surgically treated localized RCC; 283 consecutive diabetic patients treated surgically for localized RCC between January 1, 1994 and December 31, 2008 were identified. Clinicopathologic features were compared between patients exposed to metformin (n = 83, 29%) and those who were not (n = 200, 71%). Progression-free, cancer-specific, and overall survival rates were estimated with the Kaplan-Meier analysis, and Cox models were used to evaluate the association of metformin use with outcomes. Patients receiving metformin had a better renal function (median estimated glomerular filtration rate = 65 vs. 55ml/min/1.73m^2, P<0.001), performance status (Eastern Cooperative Oncology Group<1: 89% vs. 71%, P = 0.001), and lower Charlson comorbidity index (median = 2 vs. 3, P = 0.02) compared with those who did not, but were otherwise similar across other clinicopathologic features.
Conclusion: At a median postoperative follow-up of 8.1 years, patients exposed to metformin had similar 5-year progression-free (80% vs. 75%, and cancer-specific survival rates (91% vs. 81%, but significantly improved overall survival rate (79% vs. 62%. However, metformin was not independently associated with the risks of progression, RCC-specific mortality, or all-cause mortality on multivariable analyses. In this surgical cohort of diabetic patients with M0 RCC, preoperative metformin exposure was associated with improved overall survival on unadjusted analysis. Although metformin was not independently associated with oncologic or survival outcomes, future studies appear warranted.

Alternative dosing schedules for sunitinib as a treatment of patients with metastatic renal cell carcinoma. Guida FM, Santoni M, Conti A, et al. *Crit Rev Oncol Hematol*. 2014;Aug 6 [Epub ahead of print].
Summary: The approved schedule for sunitinib is 50mg/day oid in the so called "4 weeks on and two weeks off" (4/2 schedule). Since treatment with sunitinib can be maintained for years, adequate treatment of adverse events (AEs) and care for quality of life is essential. For this reason, several alternative schedules have been proposed in order to personalize sunitinib administration and reduce related toxicity. This review discusses the efficacy and tolerability of alternative regimens to the standard 4/2 schedule that have been investigated in RCC patients including schedule of 50mg/day 2-weeks on/1-week off, continuous schedule of 37.5mg daily and the "Stop and Go strategy".
Conclusion: The choice of an ideal schedule for a single individual patient seems still so far, due to the lack of biological insights that may guide the decision-making process. Data on the efficacy and tolerability of sunitinib CDD (continuous daily dosing) schedule seems to be less effective and similarly tolerated than 4/2 standard schedule, and should not be suggested for mRCC patients. Although supported by retrospective and single-center data, the 2/1 regimen seems to be effective and show better toxicity profile, compliance to treatment, and dose intensity compared to standard regimen, suggesting that 2/1 schedule may become the future sunitinib standard regimen for mRCC patients. KCJ

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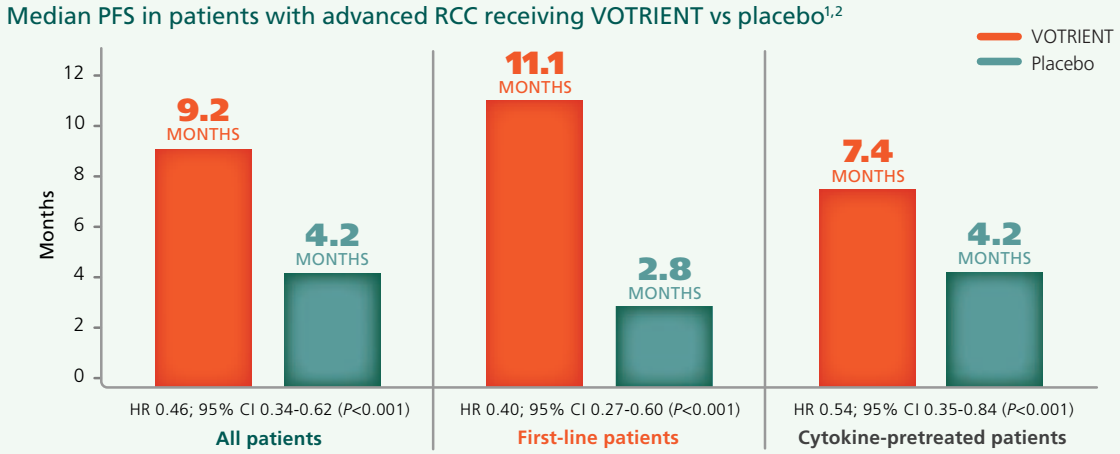

Randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of VOTRIENT in patients (N=435) with advanced RCC. Patients with locally advanced or metastatic RCC of clear cell or predominantly clear cell histology were randomized (2:1) to receive either VOTRIENT 800 mg (n=290) once daily or placebo (n=145). The study included first-line patients receiving VOTRIENT (n=155) or placebo (n=78) as well as cytokine-pretreated patients receiving VOTRIENT (n=135) or placebo (n=67).[1]

Important Safety Information for VOTRIENT (cont'd)

- **Cardiac Dysfunction:** Cardiac dysfunction, such as congestive heart failure and decreased left ventricular ejection fraction (LVEF), has occurred. In the overall safety population for RCC (N=586), cardiac dysfunction was observed in 4/586 patients (0.6%). Monitor blood pressure and manage promptly using a combination of anti-hypertensive therapy and dose modification of VOTRIENT (interruption and re-initiation at a reduced dose based on clinical judgment). Carefully monitor patients for clinical signs or symptoms of congestive heart failure. Baseline and periodic evaluation of LVEF is recommended in patients at risk of cardiac dysfunction, including previous anthracycline exposure.
- **Hemorrhagic Events:** Fatal hemorrhagic events were reported in 0.9% (5/586) of patients in the RCC trials. In the randomized RCC trial, 13% (37/290) of patients treated with VOTRIENT compared to 5% (7/145) of patients on placebo experienced at least 1 hemorrhagic event. The most common hemorrhagic events were hematuria (4%), epistaxis (2%), hemoptysis (2%), and rectal hemorrhage (1%). VOTRIENT should not be used in patients who have a history of hemoptysis, cerebral, or clinically significant gastrointestinal hemorrhage in the past 6 months.
- **Arterial Thromboembolic Events:** Arterial thromboembolic events have been observed, including fatal events (0.3%, 2/586) in the RCC trials. In the randomized RCC trial, 2% (5/290) of patients receiving VOTRIENT experienced myocardial infarction or ischemia, 0.3% (1/290) had a cerebrovascular accident, and 1% (4/290) had an event of transient ischemic attack. No arterial thromboembolic events were reported in patients who received placebo. Use with caution in patients who are at increased risk for these events and do not use in patients who have had an arterial thromboembolic event in the past 6 months.
- **Venous Thromboembolic Events:** Venous thromboembolic events (VTEs) have occurred, including venous thrombosis and fatal pulmonary emboli. In the randomized RCC trial, VTEs were reported in 1% of patients treated with VOTRIENT and in 1% of patients treated with placebo. Monitor for signs and symptoms.
- **Thrombotic Microangiopathy:** Thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) has been reported in clinical trials of VOTRIENT as monotherapy, in combination with bevacizumab, and in combination with topotecan. VOTRIENT is not indicated for use in combination with other agents. Six of the 7 TMA cases occurred within 90 days of the initiation of VOTRIENT. Improvement of TMA was observed after treatment was discontinued. Monitor for signs and symptoms of TMA. Permanently discontinue VOTRIENT in patients developing TMA. Manage as clinically indicated.
- **Gastrointestinal Perforation and Fistula:** In RCC trials, gastrointestinal perforation or fistula were reported in 0.9% (5/586) of patients receiving VOTRIENT. Fatal perforation events occurred in 0.3% (2/586) of these patients. Use with caution in patients at risk for these events and monitor for signs and symptoms.
- **Reversible Posterior Leukoencephalopathy Syndrome (RPLS):** RPLS has been reported and may be fatal. Permanently discontinue VOTRIENT in patients developing RPLS.
- **Hypertension:** Hypertension, including hypertensive crisis, has occurred in clinical trials. Hypertension occurs early in the course of treatment (approximately 40% of cases occurred by Day 9 and 90% of cases occurred in the first 18 weeks). Blood pressure should be well-controlled prior to initiating VOTRIENT, monitored early after starting treatment (no longer than 1 week), and frequently thereafter. Treat increased blood pressure promptly with standard anti-hypertensive therapy and dose reduction or interruption of VOTRIENT as clinically warranted. Discontinue VOTRIENT if there is evidence of hypertensive crisis or if hypertension is severe and persistent despite anti-hypertensive therapy and dose reduction of VOTRIENT. Approximately 1% of patients required permanent discontinuation of VOTRIENT because of hypertension.
- **Wound Healing:** VOTRIENT may impair wound healing. Interruption of therapy is recommended in patients undergoing surgical procedures; treatment with VOTRIENT should be stopped at least 7 days prior to scheduled surgery. VOTRIENT should be discontinued in patients with wound dehiscence.
- **Hypothyroidism:** Hypothyroidism was reported in 7% (19/290) of patients treated with VOTRIENT in the randomized RCC trial and in no patients receiving placebo. Monitoring of thyroid function tests is recommended.
- **Proteinuria:** In the randomized RCC trial, proteinuria was reported as an adverse reaction in 9% (27/290) of patients receiving VOTRIENT, leading to discontinuation of treatment in 2 patients. There were no reports of proteinuria in patients receiving placebo. Monitor urine protein. Interrupt treatment for 24-hour urine protein ≥3 grams and discontinue for repeat episodes despite dose reductions.
- **Infection:** Serious infections (with or without neutropenia), some with fatal outcomes, have been reported. Monitor for signs and symptoms and treat active infection promptly. Consider interruption or discontinuation of VOTRIENT.
- **Increased Toxicity with Other Cancer Therapy:** VOTRIENT is not indicated for use in combination with other agents. Increased toxicity and mortality have been observed in clinical trials administering VOTRIENT in combination with lapatinib or with pemetrexed. The fatal toxicities observed included pulmonary hemorrhage, gastrointestinal hemorrhage, and sudden death. A safe and effective combination dose has not been established with these regimens.
- **Increased Toxicity in Developing Organs:** The safety and effectiveness of VOTRIENT in pediatric patients have not been established. VOTRIENT is not indicated for use in pediatric patients. Animal studies have demonstrated pazopanib can severely affect

Once-daily oral dosing[1]

- The recommended starting dose of VOTRIENT is 800 mg once daily without food (at least 1 hour before or 2 hours after a meal). Daily dose should not exceed 800 mg
- Do not crush tablets due to the potential for increased rate of absorption, which may affect systemic exposure
- If a dose is missed, it should not be taken if it is less than 12 hours until the next dose
- In advanced RCC, initial dose reduction should be 400 mg, and additional dose decrease or increase should be in 200-mg steps based on individual tolerability
- In the Phase 3 advanced RCC trial, 42% of patients on VOTRIENT required a dose interruption; 36% of patients on VOTRIENT were dose reduced
- No dose adjustment is required in patients with mild hepatic impairment
- In patients with moderate hepatic impairment, alternatives to VOTRIENT should be considered. If VOTRIENT is used in patients with moderate hepatic impairment, the dose should be reduced to 200 mg per day
- Treatment with VOTRIENT is not recommended in patients with severe hepatic impairment
- Monitor serum liver tests before initiation of treatment and at Weeks 3, 5, 7, and 9. Thereafter, monitor at Month 3 and at Month 4, and as clinically indicated. Periodic monitoring should then continue after Month 4
- **For additional information on dosing modifications based on drug interactions, please see Sections 2.2 and 7 of accompanying Brief Summary of Prescribing Information**

VOTRIENT: Summary of serious and common adverse reactions[1]

- **Severe and fatal hepatotoxicity has been observed in clinical trials. Monitor hepatic function and interrupt, reduce, or discontinue dosing as recommended**
- **Serious adverse reactions with VOTRIENT included** hepatotoxicity, QT prolongation and torsades de pointes, cardiac dysfunction, hemorrhagic events, arterial and venous thromboembolic events, thrombotic microangiopathy, gastrointestinal perforation and fistula, reversible posterior leukoencephalopathy syndrome, hypertension, impaired wound healing, hypothyroidism, proteinuria, infection, increased toxicity with other cancer therapies, increased toxicity in developing organs, and fetal harm
- **Most common adverse reactions (≥20%)** observed in patients with advanced RCC taking VOTRIENT were diarrhea, hypertension, hair color changes (depigmentation), nausea, anorexia, and vomiting

Please see additional Important Safety Information for VOTRIENT on adjacent pages.

Please see Brief Summary of Prescribing Information, including Boxed Warning, for VOTRIENT on adjacent pages.

Pazopanib (VOTRIENT®) has a Category 1 recommendation as a first-line therapy in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for relapsed or Stage IV unresectable RCC of predominant clear cell histology.[3] NCCN Guidelines® also include therapies other than pazopanib (VOTRIENT®) as first-line treatment options.

Important Safety Information for VOTRIENT (cont'd)

organ growth and maturation during early post-natal development, and resulted in toxicity to the lungs, liver, heart, and kidney and in death. VOTRIENT may potentially cause serious adverse effects on organ development in pediatric patients, particularly in patients younger than 2 years of age.

- **Pregnancy Category D:** VOTRIENT can cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant while taking VOTRIENT.
- **Diarrhea:** Diarrhea occurred frequently and was predominantly mild to moderate in severity. Patients should be advised how to manage mild diarrhea and to notify their healthcare provider if moderate to severe diarrhea occurs so appropriate management can be implemented to minimize its impact.
- **Lipase Elevations:** In a single-arm RCC trial, increases in lipase values were observed for 27% (48/181) of patients. In the RCC trials of VOTRIENT, clinical pancreatitis was observed in <1% (4/586) of patients.
- **Pneumothorax:** Two of 290 patients treated with VOTRIENT and no patients on the placebo arm in the randomized RCC trial developed a pneumothorax.
- **Bradycardia:** In the randomized trial of VOTRIENT for the treatment of RCC, bradycardia based on vital signs (<60 beats per minute) was observed in 19% (52/280) of patients treated with VOTRIENT and in 11% (16/144) of patients on the placebo arm.
- **Drug Interactions:** Coadministration with strong CYP3A4 Inhibitors (eg, ketoconazole, ritonavir, clarithromycin) increases concentrations of pazopanib and should be avoided, but, if warranted, reduce the dose of VOTRIENT to 400 mg. Avoid grapefruit and grapefruit juice.

  Concomitant use of strong CYP3A4 inducers (eg, rifampin) should be avoided due to the potential to decrease concentrations of pazopanib. VOTRIENT should not be used in patients who cannot avoid chronic use of CYP3A4 inducers.

  Concomitant treatment with strong inhibitors of Pgp or breast cancer resistance protein (BCRP) should be avoided due to risk of increased exposure to pazopanib.

  CYP Substrates: Concomitant use of VOTRIENT with agents with narrow therapeutic windows that are metabolized by CYP3A4, CYP2D6, or CYP2C8 is not recommended. Coadministration may result in inhibition of the metabolism of these products and create the potential for serious adverse events.

  Concomitant use of VOTRIENT and simvastatin increases the incidence of ALT elevations. If a patient develops ALT elevations, follow dosing guidelines for VOTRIENT, consider alternatives to VOTRIENT, or consider discontinuing simvastatin. There are insufficient data to assess the risk of concomitant administration of alternative statins and VOTRIENT.

  Drugs That Raise Gastric pH: Avoid concomitant use of VOTRIENT with drugs that raise gastric pH (eg, esomeprazole) due to the potential to decrease concentrations of pazopanib. Consider short-acting antacids in place of proton pump inhibitors (PPIs) and H2 receptor antagonists. Separate antacid and pazopanib dosing by several hours.
- **Adverse Reactions in the Randomized RCC Trial:** Forty-two percent of patients on VOTRIENT required a dose interruption. Thirty-six percent of patients on VOTRIENT were dose reduced.

  The most common adverse reactions (≥20%) for VOTRIENT versus placebo were diarrhea (52% vs 9%), hypertension (40% vs 10%), hair color changes (depigmentation) (38% vs 3%), nausea (26% vs 9%), anorexia (22% vs 10%), and vomiting (21% vs 8%).

  Laboratory abnormalities occurring in >10% of patients and more commonly (≥5%) in patients taking VOTRIENT versus placebo included increases in ALT (53% vs 22%), AST (53% vs 19%), glucose (41% vs 33%), and total bilirubin (36% vs 10%); decreases in phosphorus (34% vs 11%), sodium (31% vs 24%), magnesium (26% vs 14%), and glucose (17% vs 3%); and leukopenia (37% vs 6%), neutropenia (34% vs 6%), thrombocytopenia (32% vs 5%), and lymphocytopenia (31% vs 24%).

References: 1. VOTRIENT® (pazopanib) Tablets [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2014. **2.** Sternberg CN, et al. *J Clin Oncol.* 2010;28(6):1061-1068. **3.** Referenced with permission from The NCCN Clinical Practice Guidelines in Oncology® for Kidney Cancer V3.2014. ©National Comprehensive Cancer Network, Inc. 2014. All rights reserved. Accessed April 30, 2014. To view the most recent and complete version of the guideline, go online to www.nccn.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN content are trademarks owned by the National Comprehensive Cancer Network, Inc.

Please see additional Important Safety Information for VOTRIENT on adjacent pages.

Please see Brief Summary of Prescribing Information, including Boxed Warning, for VOTRIENT on adjacent pages.

www.GSKSource.com **VOTRIENT.com/HCP/aRCC**

Votrient®
pazopanib tablets (200 mg)

EFFICACY LIGHTS THE WAY

BRIEF SUMMARY

VOTRIENT® (pazopanib) tablets
The following is a brief summary only; see full prescribing information for complete product information.

WARNING: HEPATOTOXICITY

Severe and fatal hepatotoxicity has been observed in clinical trials. Monitor hepatic function and interrupt, reduce, or discontinue dosing as recommended *[See Warnings and Precautions (5.1)].*

1 INDICATIONS AND USAGE
VOTRIENT is indicated for the treatment of patients with advanced renal cell carcinoma (RCC).

2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dosing: The recommended starting dose of VOTRIENT is 800 mg orally once daily without food (at least 1 hour before or 2 hours after a meal) *[see Clinical Pharmacology (12.3) of full prescribing information]*. The dose of VOTRIENT should not exceed 800 mg. Do not crush tablets due to the potential for increased rate of absorption which may affect systemic exposure *[see Clinical Pharmacology (12.3) of full prescribing information]*. If a dose is missed, it should not be taken if it is less than 12 hours until the next dose. **2.2 Dose Modification Guidelines:** In RCC, the initial dose reduction should be 400 mg, and additional dose decrease or increase should be in 200 mg steps based on individual tolerability. Hepatic Impairment: No dose adjustment is required in patients with mild hepatic impairment. In patients with moderate hepatic impairment, alternatives to VOTRIENT should be considered. If VOTRIENT is used in patients with moderate hepatic impairment, the dose should be reduced to 200 mg per day. VOTRIENT is not recommended in patients with severe hepatic impairment *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3) of full prescribing information]*. Concomitant Strong CYP3A4 Inhibitors: The concomitant use of strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir, clarithromycin) increases pazopanib concentrations and should be avoided. Consider an alternate concomitant medication with no or minimal potential to inhibit CYP3A4. If coadministration of a strong CYP3A4 inhibitor is warranted, reduce the dose of VOTRIENT to 400 mg. Further dose reductions may be needed if adverse effects occur during therapy *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3) of full prescribing information]*. Concomitant Strong CYP3A4 Inducer: The concomitant use of strong CYP3A4 inducers (e.g., rifampin) may decrease pazopanib concentrations and should be avoided. Consider an alternate concomitant medication with no or minimal enzyme induction potential. VOTRIENT should not be used in patients who cannot avoid chronic use of strong CYP3A4 inducers *[see Drug Interactions (7.1)]*.

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS
5.1 Hepatic Toxicity and Hepatic Impairment: In clinical trials with VOTRIENT, hepatotoxicity, manifested as increases in serum transaminases (ALT, AST) and bilirubin, was observed. This hepatotoxicity can be severe and fatal. Transaminase elevations occur early in the course of treatment (92.5% of all transaminase elevations of any grade occurred in the first 18 weeks) *[see Dosage and Administration (2.2)]*. In the randomized RCC trial, ALT >3 X ULN was reported in 18% and 3% of the VOTRIENT and placebo groups, respectively. ALT >10 X ULN was reported in 4% of patients who received VOTRIENT and in <1% of patients who received placebo. Concurrent elevation in ALT >3 X ULN and bilirubin >2 X ULN in the absence of significant alkaline phosphatase >3 X ULN occurred in 2% (5/290) of patients on VOTRIENT and 1% (2/145) on placebo. Two-tenths percent of the patients (2/977) from trials that supported the RCC indication died with disease progression and hepatic failure. Monitor serum liver tests before initiation of treatment with VOTRIENT and at Weeks 3, 5, 7, and 9. Thereafter, monitor at Month 3 and at Month 4, and as clinically indicated. Periodic monitoring should then continue after Month 4. Patients with isolated ALT elevations between 3 X ULN and 8 X ULN may be continued on VOTRIENT with weekly monitoring of liver function until ALT return to Grade 1 or baseline. Patients with isolated ALT elevations of >8 X ULN should have VOTRIENT interrupted until they return to Grade 1 or baseline. If the potential benefit for reinitiating treatment with VOTRIENT is considered to outweigh the risk for hepatotoxicity, then reintroduce VOTRIENT at a reduced dose of no more than 400 mg once daily and measure serum liver tests weekly for 8 weeks *[see Dosage and Administration (2.2)]*. Following reintroduction of VOTRIENT, if ALT elevations >3 X ULN recur, then VOTRIENT should be permanently discontinued. If ALT elevations >3 X ULN occur concurrently with bilirubin elevations >2 X ULN, VOTRIENT should be permanently discontinued. Patients should be monitored until resolution. VOTRIENT is a UGT1A1 inhibitor. Mild, indirect (unconjugated) hyperbilirubinemia may occur in patients with Gilbert's syndrome *[see Clinical Pharmacology (12.5) of full prescribing information]*. Patients with only a mild indirect hyperbilirubinemia, known Gilbert's syndrome, and elevation in ALT >3 X ULN should be managed as per the recommendations outlined for isolated ALT elevations. Concomitant use of VOTRIENT and simvastatin increases the risk of ALT elevations and should be undertaken with caution and close monitoring *[see Drug Interactions (7.4)]*. Insufficient data are available to assess the risk of concomitant administration of alternative statins and VOTRIENT. In patients with pre-existing moderate hepatic impairment, the starting dose of VOTRIENT should be reduced or alternatives to VOTRIENT should be considered. Treatment with VOTRIENT is not recommended in patients with pre-existing severe hepatic impairment, defined as total bilirubin >3 X ULN with any level of ALT *[see Dosage and Administration (2.2), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3) of full prescribing information]*. **5.2 QT Prolongation and Torsades de Pointes:** In the RCC trials of VOTRIENT, QT prolongation (≥500 msec) was identified on routine electrocardiogram monitoring in 2% (11/558) of patients. Torsades de pointes occurred in <1% (2/977) of patients who received VOTRIENT in the monotherapy trials. In the randomized RCC trial, 1% (3/290) of patients who received VOTRIENT had post-baseline values between 500 to 549 msec. None of the 145 patients who received placebo on the trial had post-baseline QTc values ≥500 msec. VOTRIENT should be used with caution in patients with a history of QT interval prolongation, in patients taking antiarrhythmics or other medications that may prolong QT interval, and those with relevant pre-existing cardiac disease. When using VOTRIENT, baseline and periodic monitoring of electrocardiograms and maintenance of electrolytes (e.g., calcium, magnesium, potassium) within the normal range should be performed. **5.3 Cardiac Dysfunction:** In clinical trials with VOTRIENT, events of cardiac dysfunction such as decreased left ventricular ejection fraction (LVEF) and congestive heart failure have occurred. In the overall safety population for RCC (N=586), cardiac dysfunction was observed in 0.6% (4/586) of patients without routine on-study LVEF monitoring. Blood pressure should be monitored and managed promptly using a combination of anti-hypertensive therapy and dose modification of VOTRIENT (interruption and re-initiation at a reduced dose based on clinical judgment) *[see Warnings and Precautions (5.10)]*. Patients should be carefully monitored for clinical signs or symptoms of congestive heart failure. Baseline and periodic evaluation of LVEF is recommended in patients at risk of cardiac dysfunction including previous anthracycline exposure. **5.4 Hemorrhagic Events:** Fatal hemorrhage occurred in 0.9% (5/586) in the RCC trials. In the randomized RCC trial, 13% (37/290) of patients treated with VOTRIENT and 5% (7/145) of patients on placebo experienced at least 1 hemorrhagic event. The most common hemorrhagic events in the patients treated with VOTRIENT were hematuria (4%), epistaxis (2%), hemoptysis (2%), and rectal hemorrhage (1%). Nine of 37 patients treated with VOTRIENT who had hemorrhagic events experienced serious events including pulmonary, gastrointestinal, and genitourinary hemorrhage. One percent (4/290) of patients treated with VOTRIENT died from hemorrhage compared with no (0/145) patients on placebo. In the overall safety population in RCC (N=586), cerebral/intracranial hemorrhage was observed in <1% (2/586) of patients treated with VOTRIENT. VOTRIENT has not been studied in patients who have a history of hemoptysis, cerebral, or clinically significant gastrointestinal hemorrhage in the past 6 months and should not be used in those patients. **5.5 Arterial Thromboembolic Events:** Fatal arterial thromboembolic events were observed in 0.3% (2/586) of patients in the RCC trials. In the randomized RCC trial, 2% (5/290) of patients receiving VOTRIENT experienced myocardial infarction or ischemia, 0.3% (1/290) had a cerebrovascular accident and 1% (4/290) had an event of transient ischemic attack. No arterial thromboembolic events were reported in patients who received placebo. VOTRIENT should be used with caution in patients who are at increased risk for these events or who have had a history of these events. VOTRIENT has not been studied in patients who have had an arterial thromboembolic event within the previous 6 months and should not be used in those patients. **5.6 Venous Thromboembolic Events:** In trials of VOTRIENT, venous thromboembolic events (VTE) including venous thrombosis and fatal pulmonary embolus (PE) have occurred. In the randomized RCC trial, the rate of venous thromboembolic events was 1% in both arms. There were no fatal pulmonary emboli in the RCC trial. Monitor for signs and symptoms of VTE and PE. **5.7 Thrombotic Microangiopathy:** Thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) has been reported in clinical trials of VOTRIENT as monotherapy, in combination with bevacizumab, and in combination with topotecan. VOTRIENT is not indicated for use in combination with other agents. Six of the 7 TMA cases occurred within 90 days of the initiation of VOTRIENT. Improvement of TMA was observed after treatment was discontinued. Monitor for signs and symptoms of TMA. Permanently discontinue VOTRIENT in patients developing TMA. Manage as clinically indicated. **5.8 Gastrointestinal Perforation and Fistula:** In the RCC trials, gastrointestinal perforation or fistula occurred in 0.9% (5/586) of patients receiving VOTRIENT. Fatal perforations occurred in 0.3% (2/586) of these patients in the RCC trials. Monitor for signs and symptoms of gastrointestinal perforation or fistula. **5.9 Reversible Posterior Leukoencephalopathy Syndrome:** Reversible Posterior Leukoencephalopathy Syndrome (RPLS) has been reported in patients receiving VOTRIENT and may be fatal. RPLS is a neurological disorder which can present with headache, seizure, lethargy, confusion, blindness, and other visual and neurologic disturbances. Mild to severe hypertension may be present. The diagnosis of RPLS is optimally confirmed by magnetic resonance imaging. Permanently discontinue VOTRIENT in patients developing RPLS.

5.10 Hypertension: In clinical trials, hypertension (systolic blood pressure ≥150 or diastolic blood pressure ≥100 mm Hg) and hypertensive crisis were observed in patients treated with VOTRIENT. Blood pressure should be well controlled prior to initiating VOTRIENT. Hypertension occurs early in the course of treatment (40% of cases occurred by Day 9 and 90% of cases occurred in the first 18 weeks). Blood pressure should be monitored early after starting treatment (no longer than one week) and frequently thereafter to ensure blood pressure control. Approximately 40% of patients who received VOTRIENT experienced hypertension. Grade 3 hypertension was reported in 4% to 7% of patients receiving VOTRIENT *[see Adverse Reactions (6.1)]*. Increased blood pressure should be treated promptly with standard anti-hypertensive therapy and dose reduction or interruption of VOTRIENT as clinically warranted. VOTRIENT should be discontinued if there is evidence of hypertensive crisis or if hypertension is severe and persistent despite anti-hypertensive therapy and dose reduction. Approximately 1% of patients required permanent discontinuation of VOTRIENT because of hypertension *[see Dosage and Administration (2.2)]*. **5.11 Wound Healing:** No formal trials on the effect of VOTRIENT on wound healing have been conducted. Since vascular endothelial growth factor receptor (VEGFR) inhibitors such as pazopanib may impair wound healing, treatment with VOTRIENT should be stopped at least 7 days prior to scheduled surgery. The decision to resume VOTRIENT after surgery should be based on clinical judgment of adequate wound healing. VOTRIENT should be discontinued in patients with wound dehiscence. **5.12 Hypothyroidism:** Hypothyroidism, confirmed based on a simultaneous rise of TSH and decline of T4, was reported in 7% (19/290) of patients treated with VOTRIENT in the randomized RCC trial. No patients on the placebo arm had hypothyroidism. In RCC trials of VOTRIENT, hypothyroidism was reported as an adverse reaction in 4% (26/586) of patients. Proactive monitoring of thyroid function tests is recommended. **5.13 Proteinuria:** In the randomized RCC trial, proteinuria was reported as an adverse reaction in 9% (27/290) of patients receiving VOTRIENT and in no patients receiving placebo. In 2 patients, proteinuria led to discontinuation of treatment with VOTRIENT. Baseline and periodic urinalysis during treatment is recommended with follow up measurement of 24-hour urine protein as clinically indicated. Interrupt VOTRIENT and dose reduce for 24-hour urine protein ≥3 grams; discontinue VOTRIENT for repeat episodes despite dose reductions *[see Dosage and Administration (2.2)]*. **5.14 Infection:** Serious infections (with or without neutropenia), including some with fatal outcome, have been reported. Monitor patients for signs and symptoms of infection. Institute appropriate anti-infective therapy promptly and consider interruption or discontinuation of VOTRIENT for serious infections. **5.15 Increased Toxicity with Other Cancer Therapy:** VOTRIENT is not indicated for use in combination with other agents. Clinical trials of VOTRIENT in combination with pemetrexed and lapatinib were terminated early due to concerns over increased toxicity and mortality. The fatal toxicities observed included pulmonary hemorrhage, gastrointestinal hemorrhage, and sudden death. A safe and effective combination dose has not been established with these regimens. **5.16 Increased Toxicity in Developing Organs:** The safety and effectiveness of VOTRIENT in pediatric patients have not been established. VOTRIENT is not indicated for use in pediatric patients. Based on its mechanism of action, pazopanib may have severe effects on organ growth and maturation during early post-natal development. Administration of pazopanib to juvenile rats less than 21 days old resulted in toxicity to the lungs, liver, heart, and kidney and in death at doses significantly lower than the clinically recommended dose or doses tolerated in older animals. VOTRIENT may potentially cause serious adverse effects on organ development in pediatric patients, particularly in patients younger than 2 years of age *[see Use in Specific Populations (8.4)]*. **5.17 Pregnancy:** VOTRIENT can cause fetal harm when administered to a pregnant woman. Based on its mechanism of action, VOTRIENT is expected to result in adverse reproductive effects. In pre-clinical studies in rats and rabbits, pazopanib was teratogenic, embryotoxic, fetotoxic, and abortifacient. There are no adequate and well-controlled studies of VOTRIENT in pregnant women. 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 the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while taking VOTRIENT *[see Use in Specific Populations (8.1)]*.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Potentially serious adverse reactions with VOTRIENT included hepatotoxicity, QT prolongation and torsades de pointes, cardiac dysfunction, hemorrhagic events, arterial and venous thromboembolic events, thrombotic microangiopathy, gastrointestinal perforation and fistula, Reversible Posterior Leukoencephalopathy Syndrome (RPLS), hypertension, infection, and increased toxicity with other cancer therapies *[see Warnings and Precautions (5.1-5.10, 5.14-5.15)]*. Renal Cell Carcinoma: The safety of VOTRIENT has been evaluated in 977 patients in the monotherapy trials which included 586 patients with RCC at the time of NDA submission. With a median duration of treatment of 7.4 months (range 0.1 to 27.6), the most commonly observed adverse reactions (≥20%) in the 586 patients were diarrhea, hypertension, hair color change, nausea, fatigue, anorexia, and vomiting. The data described below reflect the safety profile of VOTRIENT in 290 RCC patients who participated in a randomized, double-blind, placebo-controlled trial *[see Clinical Studies (14.1) of full prescribing information]*. The median duration of treatment was 7.4 months (range 0 to 23) for patients who received VOTRIENT and 3.8 months (range 0 to 22) for the placebo arm. Forty-two percent of patients on VOTRIENT required a dose interruption. Thirty-six percent of patients on VOTRIENT were dose reduced. Table 1 presents the most common adverse reactions occurring in ≥10% of patients who received VOTRIENT.

Table 1. Adverse Reactions Occurring in ≥10% of Patients with RCC who Received VOTRIENT

	VOTRIENT (N=290)			Placebo (N=145)		
	All Grades[a]	Grade 3	Grade 4	All Grades[a]	Grade 3	Grade 4
Adverse Reactions	%	%	%	%	%	%
Diarrhea	52	3	<1	9	<1	0
Hypertension	40	4	0	10	<1	0
Hair color changes	38	<1	0	3	0	0
Nausea	26	<1	0	9	0	0
Anorexia	22	2	0	10	<1	0
Vomiting	21	2	<1	8	2	0
Fatigue	19	2	0	8	1	1
Asthenia	14	3	0	8	0	0
Abdominal pain	11	2	0	1	0	0
Headache	10	0	0	5	0	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

Other adverse reactions observed more commonly in patients treated with VOTRIENT than placebo and that occurred in <10% (any grade) were alopecia (8% versus <1%), chest pain (5% versus 1%), dysgeusia (altered taste) (8% versus <1%), dyspepsia (5% versus <1%), dysphonia (4% versus <1%), facial edema (1% versus 0%), palmar-plantar erythrodysesthesia (hand-foot syndrome) (6% versus <1%), proteinuria (9% versus 0%), rash (8% versus 3%), skin depigmentation (3% versus 0%), and weight decreased (9% versus 3%).

Additional adverse reactions from other clinical trials in RCC patients treated with VOTRIENT are listed below:
Musculoskeletal and Connective Tissue Disorders: Arthralgia, muscle spasms.

Table 2 presents the most common laboratory abnormalities occurring in >10% of patients who received VOTRIENT and more commonly (≥5%) in patients who received VOTRIENT versus placebo.

Table 2. Selected Laboratory Abnormalities Occurring in >10% of Patients with RCC who Received VOTRIENT and More Commonly (≥5%) in Patients who Received VOTRIENT Versus Placebo

	VOTRIENT (N=290)			Placebo (N=145)		
	All Grades[a]	Grade 3	Grade 4	All Grades[a]	Grade 3	Grade 4
Parameters	%	%	%	%	%	%
Hematologic						
Leukopenia	37	0	0	6	0	0
Neutropenia	34	1	<1	6	0	0
Thrombocytopenia	32	<1	<1	5	0	<1
Lymphocytopenia	31	4	<1	24	1	0
Chemistry						
ALT increased	53	10	2	22	1	0
AST increased	53	7	<1	19	<1	0
Glucose increased	41	<1	0	33	1	0
Total bilirubin increased	36	3	<1	10	1	<1
Phosphorus decreased	34	4	0	11	0	0
Sodium decreased	31	4	1	24	4	0
Magnesium decreased	26	<1	1	14	0	0
Glucose decreased	17	0	<1	3	0	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

Diarrhea: Diarrhea occurred frequently and was predominantly mild to moderate in severity in the clinical trials. Patients should be advised how to manage mild diarrhea and to notify their healthcare provider if moderate to severe diarrhea occurs so appropriate management can be implemented to minimize its impact. Lipase Elevations: In a single-arm RCC trial, increases in lipase values were observed for 27% (48/181) of patients. Elevations in lipase as an adverse reaction were reported for 4% (10/225) of patients and were Grade 3 for 6 patients and Grade 4 for 1 patient. In the RCC trials of VOTRIENT, clinical pancreatitis was observed in <1% (4/586) of patients. Pneumothorax: Two of 290 patients treated with VOTRIENT and no patient on the placebo arm in the randomized RCC trial developed a pneumothorax. Bradycardia: In the randomized trial of VOTRIENT for the treatment of RCC, bradycardia based on vital signs (<60 beats per minute) was observed in 19% (52/280) of patients treated with VOTRIENT and in 11% (16/144) of patients on the placebo arm. Bradycardia was reported as an adverse reaction in 2% (7/290) of patients treated with VOTRIENT compared to <1% (1/145) of patients treated with placebo. **6.2 Postmarketing Experience:** The following adverse reactions have been identified during post approval use of VOTRIENT. Because these reactions are reported voluntarily from a population of uncertain size it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure. Gastrointestinal Disorders: Pancreatitis

7 DRUG INTERACTIONS

7.1 Drugs That Inhibit or Induce Cytochrome P450 3A4 Enzymes: In vitro studies suggested that the oxidative metabolism of pazopanib in human liver microsomes is mediated primarily by CYP3A4, with minor contributions from CYP1A2 and CYP2C8. Therefore, inhibitors and inducers of CYP3A4 may alter the metabolism of pazopanib. **CYP3A4 Inhibitors:** Coadministration of pazopanib with strong inhibitors of CYP3A4 (e.g., ketoconazole, ritonavir, clarithromycin) increases pazopanib concentrations and should be avoided. Consider an alternate concomitant medication with no or minimal potential to inhibit CYP3A4 *[see Clinical Pharmacology (12.3) of full prescribing information]*. If coadministration of a strong CYP3A4 inhibitor is warranted, reduce the dose of VOTRIENT to 400 mg *[see Dosage and Administration (2.2)]*. Grapefruit or grapefruit juice should be avoided as it inhibits CYP3A4 activity and may also increase plasma concentrations of pazopanib. **CYP3A4 Inducers:** CYP3A4 inducers such as rifampin may decrease plasma pazopanib concentrations. Consider an alternate concomitant medication with no or minimal enzyme induction potential. VOTRIENT should not be used if chronic use of strong CYP3A4 inducers cannot be avoided *[see Dosage and Administration (2.2)]*. **7.2 Drugs That Inhibit Transporters:** In vitro studies suggested that pazopanib is a substrate of P-glycoprotein (Pgp) and breast cancer resistance protein (BCRP). Therefore, absorption and subsequent elimination of pazopanib may be influenced by products that affect Pgp and BCRP. Concomitant treatment with strong inhibitors of Pgp or breast cancer resistance protein (BCRP) should be avoided due to risk of increased exposure to pazopanib. Selection of alternative concomitant medicinal products with no or minimal potential to inhibit Pgp or BCRP should be considered. **7.3 Effects of Pazopanib on CYP Substrates:** Results from drug-drug interaction trials conducted in cancer patients suggest that pazopanib is a weak inhibitor of CYP3A4, CYP2C8, and CYP2D6 in vivo, but had no effect on CYP1A2, CYP2C9, or CYP2C19 *[see Clinical Pharmacology (12.3) of full prescribing information]*. Concomitant use of VOTRIENT with agents with narrow therapeutic windows that are metabolized by CYP3A4, CYP2D6, or CYP2C8 is not recommended. Coadministration may result in inhibition of the metabolism of these products and create the potential for serious adverse events *[see Clinical Pharmacology (12.3) of full prescribing information]*. **7.4 Effect of Concomitant use of VOTRIENT and Simvastatin:** Concomitant use of VOTRIENT and simvastatin increases the incidence of ALT elevations. Across monotherapy studies with VOTRIENT, ALT >3 X ULN was reported in 126/895 (14%) of patients who did not use statins, compared with 11/41 (27%) of patients who had concomitant use of simvastatin. If a patient receiving concomitant simvastatin develops ALT elevations, follow dosing guidelines for VOTRIENT or consider alternatives to VOTRIENT *[see Warnings and Precautions (5.1)]*. Alternatively, consider discontinuing simvastatin *[see Warnings and Precautions (5.1)]*. Insufficient data are available to assess the risk of concomitant administration of alternative statins and VOTRIENT. **7.5 Drugs That Raise Gastric pH:** In a drug interaction trial in patients with solid tumors, concomitant administration of pazopanib with esomeprazole, a proton pump inhibitor (PPI), decreased the exposure of pazopanib by approximately 40% (AUC and C_{max}). Therefore, concomitant use of VOTRIENT with drugs that raise gastric pH should be avoided. If such drugs are needed, short-acting antacids should be considered in place of PPIs and H2 receptor antagonists. Separate antacid and pazopanib dosing by several hours to avoid a reduction in pazopanib exposure *[see Clinical Pharmacology (12.3) of full prescribing information]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy: Pregnancy Category D *[see Warnings and Precautions (5.17)]*. VOTRIENT can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of VOTRIENT in pregnant women. In pre-clinical studies in rats and rabbits, pazopanib was teratogenic, embryotoxic, fetotoxic, and abortifacient. Administration of pazopanib to pregnant rats during organogenesis at a dose level of ≥3 mg/kg/day (approximately 0.1 times the human clinical exposure based on AUC) resulted in teratogenic effects including cardiovascular malformations (retroesophageal subclavian artery, missing innominate artery, changes in the aortic arch) and incomplete or absent ossification. In addition, there was reduced fetal body weight, and pre- and post-implantation embryolethality in rats administered pazopanib at doses ≥3 mg/kg/day. In rabbits, maternal toxicity (reduced food consumption, increased post-implantation loss, and abortion) was observed at doses ≥30 mg/kg/day (approximately 0.007 times the human clinical exposure). In addition, severe maternal body weight loss and 100% litter loss were observed at doses ≥100 mg/kg/day (0.02 times the human clinical exposure), while fetal weight was reduced at doses ≥3 mg/kg/day (AUC not calculated). 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 the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while taking VOTRIENT. **8.3 Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from VOTRIENT, 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. **8.4 Pediatric Use:** The safety and effectiveness of VOTRIENT in pediatric patients have not been established. In rats, weaning occurs at day 21 postpartum which approximately equates to a human pediatric age of 2 years. In a juvenile animal toxicology study performed in rats, when animals were dosed from day 9 through day 14 postpartum (pre-weaning), pazopanib caused abnormal organ growth/maturation in the kidney, lung, liver and heart at approximately 0.1 times the clinical exposure, based on AUC in adult patients receiving VOTRIENT. At approximately 0.4 times the clinical exposure (based on the AUC in adult patients), pazopanib administration resulted in mortality. In repeat-dose toxicology studies in rats including 4-week, 13-week, and 26-week administration, toxicities in bone, teeth, and nail beds were observed at doses ≥3 mg/kg/day (approximately 0.07 times the human clinical exposure based on AUC). Doses of 300 mg/kg/day (approximately 0.8 times the human clinical exposure based on AUC) were not tolerated in 13- and 26-week studies and animals required dose reductions due to body weight loss and morbidity. Hypertrophy of epiphyseal growth plates, nail abnormalities (including broken, overgrown, or absent nails) and tooth abnormalities in growing incisor teeth (including excessively long, brittle, broken and missing teeth, and dentine and enamel degeneration and thinning) were observed in rats at doses ≥30 mg/kg/day (approximately 0.35 times the human clinical exposure based on AUC) at 26 weeks, with the onset of tooth and nail bed alterations noted clinically after 4 to 6 weeks. Similar findings were noted in repeat-dose studies in juvenile rats dosed with pazopanib beginning day 21 postpartum (post-weaning). In the post-weaning animals, the occurrence of changes in teeth and bones occurred earlier and with greater severity than in older animals. There was evidence of tooth degeneration and decreased bone growth at doses ≥30 mg/kg (approximately 0.1 to 0.2 times the AUC in human adults at the clinically recommended dose). Pazopanib exposure in juvenile rats was lower than that seen at the same dose levels in adult animals, based on comparative AUC values. At pazopanib doses approximately 0.5 to 0.7 times the exposure in adult patients at the clinically recommended dose, decreased bone growth in juvenile rats persisted even after the end of the dosing period. Finally, despite lower pazopanib exposures than those reported in adult animals or adult humans, juvenile animals administered 300 mg/kg/dose pazopanib required dose reduction within 4 weeks of dosing initiation due to significant toxicity, although adult animals could tolerate this same dose for at least 3 times as long *[see Warnings and Precautions (5.16)]*. **8.5 Geriatric Use:** In clinical trials with VOTRIENT for the treatment of RCC, 33% (196/582) of patients were aged ≥65 years. No overall differences in safety or effectiveness of VOTRIENT were observed between these patients and younger patients. However, patients >60 years of age may be at greater risk for an ALT >3 X ULN. Other reported clinical experience has not identified differences in responses between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. **8.6 Hepatic Impairment:** In clinical studies for VOTRIENT, patients with total bilirubin ≤1.5 X ULN and AST and ALT ≤2 X ULN were included *[see Warnings and Precautions (5.1)]*. An analysis of data from a pharmacokinetic study of pazopanib in patients with varying degrees of hepatic dysfunction suggested that no dose adjustment is required in patients with mild hepatic impairment [either total bilirubin within normal limit (WNL) with ALT > ULN or bilirubin >1 X to 1.5 X ULN regardless of the ALT value]. The maximum tolerated dose in patients with moderate hepatic impairment (total bilirubin >1.5 X to 3 X ULN regardless of the ALT value) was 200 mg per day (N=11). The median steady-state C_{max} and $AUC_{(0-24)}$ achieved at this dose was approximately 40% and 29%, respectively, of that seen in patients with normal hepatic function at the recommended daily dose of 800 mg. The maximum dose explored in patients with severe hepatic impairment (total bilirubin >3 X ULN regardless of the ALT value) was 200 mg per day (N=14). This dose was not well tolerated. Median exposures achieved at this dose were approximately 18% and 15% of those seen in patients with normal liver function at the recommended daily dose of 800 mg. Therefore, VOTRIENT is not recommended in these patients *[see Clinical Pharmacology (12.3) of full prescribing information]*. **8.7 Renal Impairment:** Patients with renal cell cancer and mild/moderate renal impairment (creatinine clearance ≥30 mL/min) were included in clinical trials for VOTRIENT. There are no clinical or pharmacokinetic data in patients with severe renal impairment or in patients undergoing peritoneal dialysis or hemodialysis. However, renal impairment is unlikely to significantly affect the pharmacokinetics of pazopanib since <4% of a radiolabeled oral dose was recovered in the urine. In a population pharmacokinetic analysis using 408 patients with various

cancers, creatinine clearance (30-150 mL/min) did not influence clearance of pazopanib. Therefore, renal impairment is not expected to influence pazopanib exposure, and dose adjustment is not necessary.

10 OVERDOSAGE

Pazopanib doses up to 2,000 mg have been evaluated in clinical trials. Dose-limiting toxicity (Grade 3 fatigue) and Grade 3 hypertension were each observed in 1 of 3 patients dosed at 2,000 mg daily and 1,000 mg daily, respectively. Treatment of overdose with VOTRIENT should consist of general supportive measures. There is no specific antidote for overdosage of VOTRIENT. Hemodialysis is not expected to enhance the elimination of VOTRIENT because pazopanib is not significantly renally excreted and is highly bound to plasma proteins.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility:

Carcinogenicity studies with pazopanib have not been conducted. However, in a 13-week study in mice, proliferative lesions in the liver including eosinophilic foci in 2 females and a single case of adenoma in another female was observed at doses of 1,000 mg/kg/day (approximately 2.5 times the human clinical exposure based on AUC). Pazopanib did not induce mutations in the microbial mutagenesis (Ames) assay and was not clastogenic in both the in vitro cytogenetic assay using primary human lymphocytes and in the in vivo rat micronucleus assay. Pazopanib may impair fertility in humans. In female rats, reduced fertility including increased pre-implantation loss and early resorptions were noted at dosages ≥30 mg/kg/day (approximately 0.4 times the human clinical exposure based on AUC). Total litter resorption was seen at 300 mg/kg/day (approximately 0.8 times the human clinical exposure based on AUC). Post-implantation loss, embryolethality, and decreased fetal body weight were noted in females administered doses ≥10 mg/kg/day (approximately 0.3 times the human clinical exposure based on AUC). Decreased corpora lutea and increased cysts were noted in mice given ≥100 mg/kg/day for 13 weeks and ovarian atrophy was noted in rats given ≥300 mg/kg/day for 26 weeks (approximately 1.3 and 0.85 times the human clinical exposure based on AUC, respectively). Decreased corpora lutea was also noted in monkeys given 500 mg/kg/day for up to 34 weeks (approximately 0.4 times the human clinical exposure based on AUC). Pazopanib did not affect mating or fertility in male rats. However, there were reductions in sperm production rates and testicular sperm concentrations at doses ≥3 mg/kg/day, epididymal sperm concentrations at doses ≥30 mg/kg/day, and sperm motility at ≥100 mg/kg/day following 15 weeks of dosing. Following 15 and 26 weeks of dosing, there were decreased testicular and epididymal weights at doses of ≥30 mg/kg/day (approximately 0.35 times the human clinical exposure based on AUC); atrophy and degeneration of the testes with aspermia, hypospermia and cribiform change in the epididymis was also observed at this dose in the 6-month toxicity studies in male rats.

17 PATIENT COUNSELING INFORMATION

See Medication Guide. The Medication Guide is contained in a separate leaflet that accompanies the product. However, inform patients of the following:

- Therapy with VOTRIENT may result in hepatobiliary laboratory abnormalities. Monitor serum liver tests (ALT, AST, and bilirubin) prior to initiation of VOTRIENT and at Weeks 3, 5, 7, and 9. Thereafter, monitor at Month 3 and at Month 4, and as clinically indicated. Inform patients that they should report signs and symptoms of liver dysfunction to their healthcare provider right away.
- Prolonged QT intervals and torsades de pointes have been observed. Patients should be advised that ECG monitoring may be performed. Patients should be advised to inform their physicians of concomitant medications.
- Cardiac dysfunction (such as CHF and LVEF decrease) has been observed in patients at risk (e.g., prior anthracycline therapy) particularly in association with development or worsening of hypertension. Patients should be advised to report hypertension or signs and symptoms of congestive heart failure.
- Serious hemorrhagic events have been reported. Patients should be advised to report unusual bleeding.
- Arterial thrombotic events have been reported. Patients should be advised to report signs or symptoms of an arterial thrombosis.
- Reports of pneumothorax and venous thromboembolic events including pulmonary embolus have been reported. Patients should be advised to report if new onset of dyspnea, chest pain, or localized limb edema occurs.
- Advise patients to inform their doctor if they have worsening of neurological function consistent with RPLS (headache, seizure, lethargy, confusion, blindness, and other visual and neurologic disturbances).
- Hypertension and hypertensive crisis have been reported. Patients should be advised to monitor blood pressure early in the course of therapy and frequently thereafter and report increases of blood pressure or symptoms such as blurred vision, confusion, severe headache, or nausea and vomiting.
- GI perforation or fistula has occurred. Advise patients to report signs and symptoms of a GI perforation or fistula.
- VEGFR inhibitors such as VOTRIENT may impair wound healing. Advise patients to stop VOTRIENT at least 7 days prior to a scheduled surgery.
- Hypothyroidism and proteinuria have been reported. Advise patients that thyroid function testing and urinalysis will be performed during treatment.
- Serious infections including some with fatal outcomes have been reported. Advise patients to promptly report any signs or symptoms of infection.
- Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant.
- Gastrointestinal adverse reactions such as diarrhea, nausea, and vomiting have been reported with VOTRIENT. Patients should be advised how to manage diarrhea and to notify their healthcare provider if moderate to severe diarrhea occurs.
- Patients should be advised to inform their healthcare providers of all concomitant medications, vitamins, or dietary and herbal supplements.
- Patients should be advised that depigmentation of the hair or skin may occur during treatment with VOTRIENT.
- Patients should be advised to take VOTRIENT without food (at least 1 hour before or 2 hours after a meal).

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