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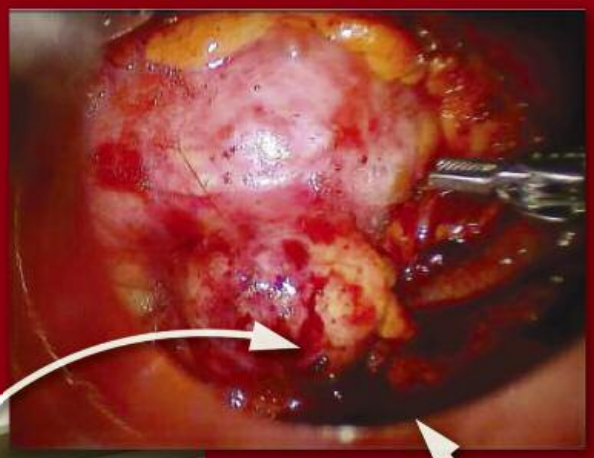
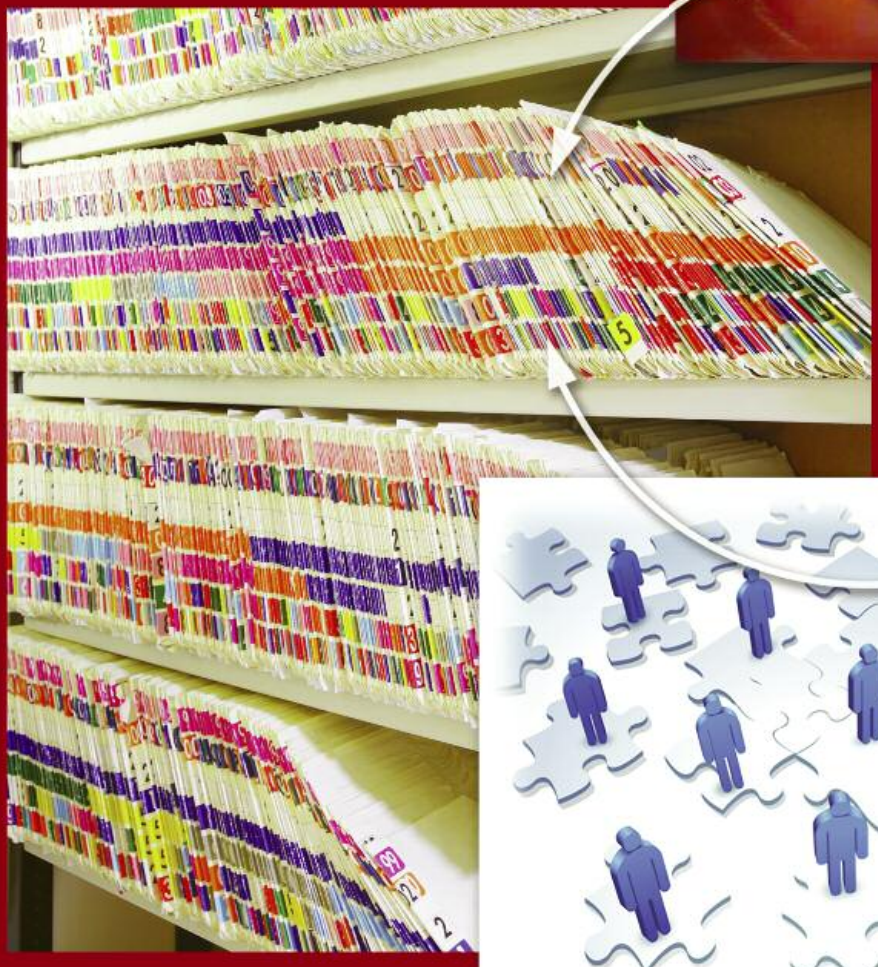
Active Surveillance for Small Renal Masses: Take-Home Messages From the DISSRM Registry

Highlights From ASCO 2016: Analyses of All RCC Sessions

Case Report of Primary Renal Carcinoid Tumor





See About the Cover, Page 42

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

Important Safety Information and Indication

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.

Inlyta®
axitinib 1mg and 5mg tablets
CONTINUE THE FIGHT

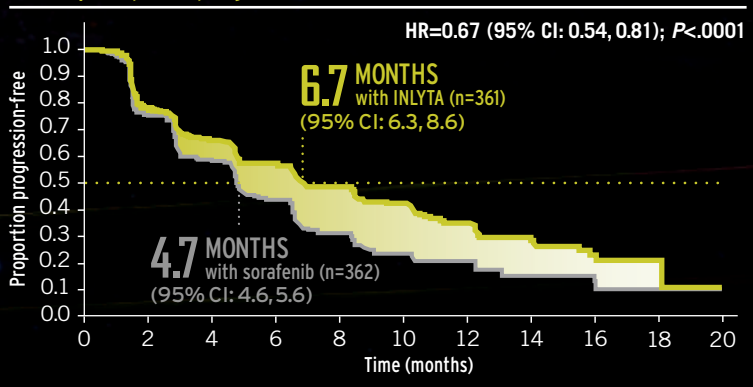
GIVE THEM A FIGHTING SECOND CHANCE

INLYTA IS INDICATED FOR THE TREATMENT OF ADVANCED RCC AFTER FAILURE OF ONE PRIOR SYSTEMIC THERAPY.

INLYTA—the ONLY approved treatment option to demonstrate superior PFS vs a TKI, sorafenib, in a phase 3 trial for 2nd-line mRCC*

*Based on MEDLINE® literature review for phase 3 trials in mRCC as of February 2016. TKI=tyrosine kinase inhibitor.

Primary endpoint: progression-free survival (PFS)



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 [54%, 3%, 8%, and 35% of patients in each of the treatment arms, respectively]). Patients were randomized 1:1 to either INLYTA 5 mg twice daily (n=361) or sorafenib 400 mg twice daily (n=362), 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]

Axitinib has a National Comprehensive Cancer Network® (NCCN®) category 1 recommendation as a subsequent therapy option, after either a TKI or a cytokine therapy in patients with advanced predominantly clear-cell RCC.[3]

INLYTA has been approved by the FDA for the treatment of advanced renal cell carcinoma (RCC) after failure of one prior systemic therapy.

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 (55% vs 53%), hypertension (40% vs 29%), fatigue (39% vs 32%), decreased appetite (34% vs 29%), nausea (32% vs 22%), dysphonia (31% vs 14%), hand-foot syndrome (27% vs 51%), weight decreased (25% vs 21%), vomiting (24% vs 17%), asthenia (21% vs 14%), and constipation (20% vs 20%).

The **most common (≥10%) grade 3/4 AEs** occurring in patients receiving INLYTA (vs sorafenib) were hypertension (16% vs 11%), diarrhea (11% vs 7%), and fatigue (11% vs 5%).

The **most common (≥20%) lab abnormalities** occurring in patients receiving INLYTA (all grades, vs sorafenib) included increased creatinine (55% vs 41%), decreased bicarbonate (44% vs 43%), hypocalcemia (39% vs 59%), decreased hemoglobin (35% vs 52%), decreased lymphocytes (absolute) (33% vs 36%), increased ALP (30% vs 34%), hyperglycemia (28% vs 23%), increased lipase (27% vs 46%), increased amylase (25% vs 33%), increased ALT (22% vs 22%), and increased AST (20% vs 25%).

Indication

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

Please see Brief Summary on the following pages.

March 2016

Pfizer U.S. Pharmaceuticals

References: 1. Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. *Lancet*. 2011;378(9807):1931-1939. **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.2.2016. © National Comprehensive Cancer Network, Inc. 2015. All rights reserved. Accessed January 28, 2016. 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; NCCN=National Comprehensive Cancer Network.

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

About the Cover
The interactive images depict how a Johns Hopkins registry addresses key issues and questions involving active surveillance for the small renal mass (photo). Medical records provide a data base of patients from which patient selection is made for inclusion in the DISSRM Registry. Figures on the right suggest concept of how the registry could be applied to stratify patients to surveillance or intervention.

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KCJ EDITOR'S MEMO

Welcome to the Virtual World of ASCO and Beyond

Remember when virtual meetings were the figment of some webmaster's imagination? Many attendees at the 2016 meeting of the American Society of Clinical Oncology (ASCO) remember sessions not much more than a few years ago where we picked up thick books of abstracts and related material that everyone carried around to various sessions. This was before technological advances like the flash drive and other novelties created the virtual meeting revolution, a parallel universe, so to speak, that has not only become a huge benefit of ASCO but other medical meetings as well.

If you missed this year's meeting—or even if you attended—there are abundant resources available, enabling you to review or keep pace with nearly all of the presentations and selected sessions. Although much of the technology that supports virtual meeting tools is not new, the underlying software and infrastructure are maturing quickly, in some cases allowing medical education to benefit from real-time interaction for remote programs as well as offering new opportunities for traditional, residential education.

Although the actual experience of ASCO is hard to duplicate—even with advances in virtual meeting presentations—the online offerings, not only from ASCO but from other sources as well, are a tremendous asset for following new information. On the ASCO website the Virtual Meeting grants you full access to *every* session—you can watch and listen to more than 150 captured sessions on your computer, tablet, or mobile device. As ASCO promotes its service: "Virtual Meeting is the next best thing to being at the 2016 Annual Meeting in person, and without travel expense or time away from work."

But virtual analyses based on presentations at the ASCO meeting are not limited to what's on the ASCO website. If you want quick synopses of new developments, you can benefit from the Oncology Business Review (OBR) offerings. If you visit this website, http://obroncology.com/VideoCenter/?cat=Kidney%20(Renal%20Cell)%20Cancer, you may find my discussions useful regarding the impact of recent approvals of two new drugs for renal cell carcinoma (RCC)—lenvatinib and cabozantinib. These brief yet illuminating tutorials provide a rapid (about 60 seconds in some cases) overview

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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.

All material reproduced from previously published, copyrighted material should contain a full credit line acknowledging the original source. The author is responsible for obtaining this permission.

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.

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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.

DNA Methylation Signature Reveals Cell Ontogeny of Renal Cell Carcinomas. Malouf GG, Su X, Zhang J, Creighton CJJ, et al. *Clin Cancer Res*. 2016 Jun 2; pii: clincanres. 1217.2015

Summary: DNA methylation is a heritable covalent modification that is developmentally regulated and is critical in tissue-type definition. Although genotype-phenotype correlations have been described for different subtypes of renal cell carcinoma (RCC), it is unknown if DNA methylation profiles correlate with morphological or ontology based phenotypes. This report tested the hypothesis that DNA methylation signatures can discriminate between putative precursor cells in the nephron. The authors performed deep profiling of DNA methylation and transcriptome in diverse histopathological RCC subtypes and validated DNA methylation in an independent dataset as well as in The Cancer Genome Atlas Clear Cell and Chromophobe Renal Cell Carcinoma Datasets. The data provide the first mapping of methylome epi-signature and indicates that RCC subtypes can be grouped into two major epi-clusters: C1 which encompasses clear-cell RCC, papillary RCC, mucinous and spindle cell carcinomas and translocation RCC; C2 which comprises oncocytoma and chromophobe RCC. Interestingly, C1 epi-cluster displayed three fold more hypermethylation as compared to C2 epi-cluster. Of note, differentially methylated regions between C1 and C2 epi-clusters occur in gene bodies and intergenic regions, instead of gene promoters. Transcriptome analysis of C1 epi-cluster suggests a functional convergence on Polycomb targets, whereas C2 epi-cluster displays DNA methylation defects. Furthermore, the epigenetic ontogeny signature is associated with worse outcomes of patients with clear-cell RCC.

Conclusion: The data define the epi-clusters that can discriminate between distinct RCC subtypes and for the first time define the epigenetic basis for proximal versus distal tubule derived kidney tumors.

The Evolution of Systemic Therapy in Metastatic Renal Cell Carcinoma. Hutson TE, Thoreson GR, Figlin RA, et al. *Am Soc Clin Oncol Educ Book*. 2016; 35:113-7. doi: 10.14694/EDBK-158892.

Summary: The treatment landscape for RCC is a dynamic process that has seen considerable change in recent years. We have seen a rebirth of original breakthroughs with immune checkpoint inhibitors showing promise in patients with treatment-refractory disease. The optimal sequencing of treatments and incorporation of novel therapeutics are actively being investigated and have yet to be determined. The clinical challenges of this evolving treatment paradigm can be attributed to cost considerations, toxicity, and defining endpoints in the management of advanced RCC.

Conclusion: As novel therapeutics emerge, finding the optimal treatment regimen for patients will have an increasing focus on patient-centered outcomes and improvement in quality of life in addition to improving survival.

Renal Cancer Stem Cells: Characterization and Targeted Therapies. Peired AJ, Sisti A, Romagnani P. *Stem Cells Int*. 2016;2016:8342625. doi: 10.1155/2016/8342625. Epub 2016 May 15

Summary: Tumors are heterogeneous and are composed of differentiated cancer cells, stromal cells,and cancer stem cells (CSCs). CSCs possess two main properties: self-renewal and proliferation. Additionally, they can generate new tumors once transplanted into immuno-deficient mice. Several approaches have been described to identify them, through the expression of cell markers, functional assays, or a combination of both. As CSCs are involved in the resistance mechanisms to radio- and chemotherapies, several new strategies have been proposed to directly target CSCs in RCC. One approach drives CSCs to differentiate into cancer cells sensitive to conventional treatments, while the other proposes to eradicate them selectively.

Conclusion: A series of innovative therapies aiming at eliminating CSCs have been designed to treat other types of cancer and have not been experimented with on RCC yet, but they reveal themselves to be promising. CSCs are an important player in carcinogenesis and represent a valid target for therapy in RCC patients.

Cabozantinib Versus Everolimus in Advanced Renal Cell Carcinoma (METEOR): Final Results From a Randomised, Open-Label, Phase 3 Trial. Choueiri TK, Escudier B, Powles T, et al. *Lancet Oncol*. 2016 Jun 3. pii: S1470-2045(16)30107-3. doi: 10.1016/S1470-2045(16)30107-3.

Summary: Cabozantinib is an oral inhibitor of tyrosine kinases including MET, VEGFR, and AXL. The randomized phase 3 METEOR trial compared the efficacy and safety of cabozantinib versus the mTOR inhibitor everolimus in patients with advanced RCC who progressed after previous VEGFR tyrosine-kinase inhibitor treatment. Here, we report the final overall survival results from this study based on an unplanned second interim analysis. In this open-label, randomized phase 3 trial, the authors randomly assigned (1:1) patients aged 18 years and older with advanced or metastatic clear-cell RCC, measurable disease, and previous treatment with one or more VEGFR tyrosine-

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

Two New Drugs Approved for Kidney Cancer—Cabozantinib and Lenvatinib

Treatment options in renal cell carcinoma (RCC) have expanded dramatically with the FDA approval of two drugs for advanced disease. The FDA approved lenvatinib (Lenvima), a multiple receptor tyrosine kinase inhibitor, in combination with everolimus for the treatment of patients with advanced RCC previously treated with an anti-angiogenic therapy. It also approved cabozantinib (Cabomytex), another agent for this setting.

Lenvatinib Approval Approval of lenvatinib was based on impressive results of the registration study (Study 205), in which the once daily combination of 18 mg Lenvima and 5 mg everolimus demonstrated substantial improvement in progression-free survival (PFS), powerful objective response rate (ORR) and clinically meaningful overall survival (OS) when compared with everolimus alone, a standard of care for patients with aRCC who have received prior anti-angiogenic therapy.

"Lenvatinib plus everolimus is the first and only FDA-approved regimen that successfully combines treatments that employ tyrosine kinase and mTOR inhibition, the primary targets of advanced RCC treatment for the past decade," said Robert Motzer, MD Memorial Sloan Kettering Cancer Center, New York, and the principal investigator of the study. "This combination regimen led to enhanced efficacy and helped patients with advanced RCC live longer without disease progression or death than those treated with everolimus alone. These noteworthy findings advance the treatment paradigm for this patient population."

In Study 205, a Phase 2 trial, Lenvima and everolimus (LEN+EVE) resulted in a median PFS nearly three times that of everolimus alone. The median PFS in patients treated with the combination (n=51) was 14.6 months compared with 5.5 months (95% CI: 3.5–7.1) for those treated with everolimus alone (n=50). The combination regimen resulted in a 63% reduction in the risk of disease progression or death compared with everolimus alone. The treatment effect of the combination on PFS was supported by a retrospective independent review.

The objective response rate was 37% in patients treated with the combination regimen (35% partial response + 2% complete response) compared to 6% (all partial response) in patients treated with everolimus alone. The patients who received LEN+EVE experienced a 10.1-month increase in median OS compared with those who received everolimus monotherapy (25.5 months versus 15.4 months. This OS analysis was conducted when 63% of deaths had occurred in the combination arm and 74% of deaths had occurred in the everolimus arm.

Cabozantinib Approval Cabozantiib is the first therapy to demonstrate in a phase 3 trial for patients with advanced RCC, robust and clinically meaningful improvements in all three key efficacy parameters — overall survival, progression-free survival (PFS) and objective response rate.

"The efficacy profile demonstrated by Cabomytex in the METEOR trial, now complemented by the overall survival benefit, is highly compelling," said Toni Choueiri, MD, Clinical Director, Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute. "Cabomytex is distinct from other approved treatment options, as it targets multiple tyrosine kinases involved in the development of RCC, including MET, AXL and three VEGF receptors. At the same time, physicians are very familiar with this class of drug and how to use dose adjustments to balance safety and efficacy. The approval of Cabomytex is wonderful news for physicians who are looking for a new option for their previously treated patients with advanced kidney cancer."

Approval of the drug is based on results of the phase 3 METEOR trial, which met its primary endpoint of improving progression-free survival. Compared with everolimus, a standard of care therapy for second-line RCC, Cabomytex was associated with a 42% reduction in the rate of disease progression or death. Median PFS for cabozantinib was 7.4 months versus 3.8 months for everolimus (HR=0.58, 95% CI 0.45-0.74, P<0.0001). Cabomytex also significantly improved the objective response rate compared with everolimus.

New Phase 3 Trial Launched for Tivozanib

CAMBRIDGE, MA—The first patient has been dosed in the Aveo Oncology's pivotal TIVO-3 trial, a randomized, controlled, multi-center, open-label study to compare tivozanib to sorafenib in subjects with refractory advanced renal cell carcinoma (RCC). Tivozanib is an oral, once-daily, vascular endothelial growth factor (VEGF) tyrosine kinase inhibitor (TKI). The trial represents a renewed effort by Aveo to reintroduce the agent after its initial discouraging results at the FDA several years ago based on methodological issues.

The Phase 3 trial is expected to enroll approximately 322 patients with recurrent or metastatic RCC who have failed at least two prior regimens, including VEGFR-TKI therapy (other than sorafenib). Eligible patients may also have received checkpoint inhibitor therapy in earlier lines of treatment. Patients will be randomized 1:1 to receive either tivozanib or sorafenib, with no crossover between arms. The primary endpoint of the study is progression free survival. Secondary endpoints include overall survival, overall response rate, and safety and tolerability. Top line readout of the study is currently projected for the first quarter of 2018.

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Active Surveillance for Small Renal Masses: a Review of the Literature and a Focus on the DISSRM Registry

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Introduction

Small renal masses (SRM), or solid cortical neoplasms of the kidney less than 4 cm, are the most commonly diagnosed renal masses and are most-often detected incidentally when working up another issue.[1] The recent increased incidence in SRM is believed to be due to an increased utilization of trans-axial imaging. The greatest issue in the management of the SRM is biological heterogeneity. Upwards of 70-80% of SRM are malignant, the majority of which are believed to be low-grade, indolent tumors. The remaining 20-30% are frankly benign masses.[2-4] It is often difficult to determine preoperatively where a particular SRM falls, and it is estimated that almost 6,000 patients yearly in the US undergo an unnecessary kidney operation for a benign mass.[5] Conversely, some SRM are high-grade or locally advanced (pT3-4) with tangible metastatic potential.[4] With few curative options for metastatic disease, the dichotomy between the indolent and fatal creates a management dilemma. Active surveillance (AS) has emerged as a management strategy to address the high proportion of patients with low-grade or indolent disease [6]; the salient data regarding AS will be discussed in this review.

Predictors of Malignancy and High-Risk Malignancy

Roughly 78-80% of SRM 1-4 cm in size are malignant.[2-4] Of malignant masses 2-3 cm in size, 6.5-27.5%, are high grade, depending on RCC subtype; of masses 3-4 cm in size, 18.7-40% are high grade.[3] However, only 3% of masses 3 cm or smaller are metastatic at diagnosis.[7] Furthermore, of 3-4 cm masses that are removed surgically, only 2% will develop into metastatic disease after 3 years of follow up.[8] There are a number of benign entities that present as SRM in the kidney, the most common being oncocytomas or fat-poor angiomyolypomas.[9]

A number of studies[10,11] have examined the rates of benign and malignant tumors based on clinical characteristics; however, many have outcomes dominated by larger, aggressive cancers. Looking at clinical predictors of malignancy in the SRM population, Ball et al. recently determined that of clinical stage T1a tumors going on to partial nephrectomy, risk factors for both malignancy and high-risk malignancy (grade 3-4 or upstaging to pathologic stage T3a at nephrectomy) included male sex, tumor size 3 cm or larger, and nephrometry score 8 or higher.[12] For a woman with a tumor smaller than 3 cm and a nephrometry score less than 8, the risk of malignancy was 64%; for a man with a tumor 3 cm or larger and a nephrometry score of 8 or greater, the risk of malignancy was 89%.[12]

With the clinical heterogeneity of SRM, percutaneous renal biopsy (PRB) is a logical adjunct in differentiating benign from malignant disease and high-risk from indolent cancer. Indeed, PRB has excellent performance characteristics – according to a recent systematic review and meta-analysis[13] and an Agency for Healthcare Research and Quality (AHRQ) systematic review[14] on the subject, PRB has a sensitivity and specificity above 90%; and there is good agreement between the RCC subtype diagnosed from the PRB and surgical specimen, with a kappa of 0.683.[13] However, the issue with PRB lies in the significant non-diagnostic rate (14%), poor negative predictive value (68%) and inability to reliably distinguish high-grade tumors, with 20.5% of biopsy diagnoses having Fuhrman upgrading in the nephrectomy specimen.[14] This last point may be due, in part, to intra-tumoral grade heterogeneity,[15] whereby PRB may be missing the high grade components of a tumor.

Furthermore, certain tumors pose a particular challenge to PRB, for instance those tumors with oncocytic features, which may represent multiple different eosinophilic variants of RCC as well as benign oncocytoma; these are often difficult to differentiate with the

Keywords: Small renal mass, percutaneous renal biopsy, Delayed Intervention and Surveillance for Small Renal Masses DISSRM Registry, active surveillance, Renal Cell Consortium of Canada.

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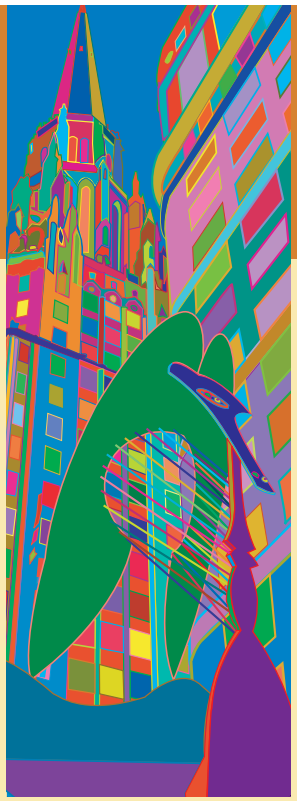

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limited tissue provided in a PRB specimen.[16] Despite these limitations, the rate of Clavien 2 or higher complications has been found to be very low.[13] The AHRQ systematic review[14] shows low complication rates, including hematoma in 4.9%, severe pain in 1.2%, gross hematuria in 1%, pneumothorax in 0.6%, and hemorrhage in 0.4%.

Use of PRB to Stratify Patients to Surveillance or Intervention

Illustrating the use of PRB in stratifying patients with SRM to AS or primary surgical intervention (PI), Halverson et al. reported an interesting study[17] of 151 patients undergoing nephrectomy for an SRM who all had preoperative PRB. Based on the PRB results and tumor and patient clinical characteristics, patients were assigned – hypothetically, since every patient had nephrectomy – to AS or PI treatment groups using a treatment algorithm developed at that institution based on consensus opinion.[17] Pathologic diagnosis of the surgical specimen was used to determine the accuracy of the algorithm.[17] They determined that 31% of those assigned to AS would have been assigned to PI, had the PRB been accurate.[17] The most common inaccuracy of PRB pathology was under-grading of clear cell RCC.[17]

Given the relatively high risk that a SRM will harbor malignant disease, and the possibility for false negative results and under-grading with PRB, we recommend that PRB should be limited to those patients who are most likely to benefit from its results, namely those trying to decide between AS and PI. Younger, healthier patients who would have minimal risk from undergoing a minimally-invasive partial nephrectomy should be wary of this significant negative predictive value. On the other hand, as will be shown in the review of AS data below, patients with limited life expectancy who are poor surgical candidates are likely to not die of their SRM but of their other comorbidities, and would thus likely fair best with an AS approach to treatment regardless of PRB result. The patient in the middle of those two extremes is the one likely to benefit from PRB, since that added information may help influence a management decision. Additionally, one demographic in particular, young women with SRM, has an exceedingly high rate of benign disease[18-20]; patients in that demographic should consider biopsy prior to any intervention. This strategy may change with developing techniques of molecular and genetic analysis of PRB specimens, discussed in greater detail below.

"Given the relatively high risk that a SRM will harbor malignant disease, and the possibility for false negative results and under-grading with PRB, we recommend that PRB should be limited to those patients who are most likely to benefit from its results, namely those trying to decide between AS and PI. Younger, healthier patients who would have minimal risk from undergoing a minimally-invasive partial nephrectomy should be wary of this significant negative predictive value."

Natural History of Small Renal Masses on Active

Epidemiologic studies have shown that RCC incidence is highest in those in their 7th and 8th decades,[21] when comorbid conditions are frequently present. AS is a management strategy largely intended for those with limited life expectancy and competing comorbidities. The goal of AS is to defer surgical therapy in those who are unlikely to benefit from it and to identify those with more aggressive pathologies who may benefit from more aggressive therapy. In order to understand why a patient might benefit from AS, it is important to understand the natural history of SRM on AS.

A number of retrospective studies have characterized this natural history, which was recently reviewed by Borghesi et al. (22).[22] The mean ages of the patients in those reviewed trials ranged from late 60s to 80s.[22] Study duration varied from 24 to 91.5 months.[22] PRB rates were widely variable across the series, ranging from 0 to 55.6%.[22] Linear growth rate ranged from 0.1 to 0.4 cm per year, and failure of AS, with a movement to delayed surgical intervention (DI), ranged widely as well, from 5 to 39%.[22] Metastasis during the follow-up periods was rare: 0-5.7%.[22]

A recent large meta-analysis[23] found the metastasis rate to be around 2%, and found that those who develop metastases have larger initial tumor sizes (4.3 cm vs. 2.3 cm) and faster tumor growth rates (0.8 cm per year vs. 0.4 cm per year) than those who do not develop metastases; furthermore, metastasis was not observed in those without radiologic evidence of tumor growth. Adding to this data, Lee et al.[24]recently reported on 111 patients with small RCCs initially followed with AS but going on to get nephrectomy. With a median initial tumor size of 1.45 cm, they found a median growth rate of 0.28 cm per year, which did not vary by histologic subtype but did vary by Fuhrman grade, with higher grades having faster growth rates.

Retrospective series have been criticized for their bias, since (especially if biopsy is not undertaken) they often include patients with benign and malignant pathology, and those who develop metastatic disease or die may be lost to follow up.[6] Nonetheless, they do provide some credence to the idea that small, slow growing SRMs are frequently indolent and larger, faster growing SRMs are at higher risk for having aggressive pathology.

Prospective Studies of Active Surveillance

There are currently two large, prospective studies of AS worldwide – one from Canada (Renal Cell Consortium of Canada (RCCC)) and the other in US-based centers (Delayed Intervention and Surveillance for Small Renal Masses (DISSRM)).[2,25] Each study and protocol have important similarities and distinctions (**Table**). Each includes a cohort of patients on AS for a SRM, and reports data on rates of crossover to DI and progression to locally advanced and metastatic disease. These data validate similar indices reported by retrospective studies of the natu-

Table. Prospective studies of active surveillance for small renal masses: basic setup and results.

	RCCC[2]	DISSRM[25]
Region	Canada	United States
Number of centers	8	3
Start of enrollment	2004	2009
Year of last published results	2011	2015
Eligibility criteria	cT1aN0M0 mass on imaging, deemed not fit for surgery	18 years or older, cT1aN0M0 mass on imaging, no personal history of RCC or a known familial RCC syndrome
Study arms	AS	AS, PI, DI
Surveillance protocol	Biopsy is recommended. CT, MRI, or ultrasound at 3 and 6 months, then every 6 months until year 3, and then yearly. Tumors that are benign on biopsy are followed yearly.	Biopsy is offered. Ultrasound (recommended; or CT, or MRI) every 6 months for the first 2 years and every 1 year thereafter, with trans-axial imaging if ultrasound incompletely images the mass or there is an unexpected change in the growth rate or changes in the qualitative appearance of the mass. Biopsy results do not change surveillance protocol.
Definition of local progression	Tumor diameter of 4 cm or greater, or doubling of tumor volume in 12 or fewer months	Maximum diameter larger than 4.0 cm, a growth rate that exceeds 0.5 cm/year, hematuria suspected to be from the SRM
Number of patients in last published results	178 (AS only)	PI: 274 AS: 223 (of which 21 undergo DI)
Follow-up period in last published X growth rate that exceeds 0.5 cm/year, hema	28 (mean)	25 (median)
Rate of PRB at enrollment in last published results (%)	55.6	6.4
Tumor growth rate in last published results (cm/year)	0.13 (mean)	0.11 (median)
Rate of local progression of AS arm in last published results (%)	12	16
Rate of metastatic disease in last published results (%)	AS arm: 1.1	AS arm: 0 PI arm: 0.7 DI arm: 0
Survival outcomes	Not reported	5-year OS for PI=92%; AS=75% 5-year CSS for PI=99%; AS=100%

ral history of SRM on AS, but, because of the prospective nature, includes information about patients leaving the study, a factor that may play a large part in the risk for bias in the retrospective series. Furthermore, for the first time in the literature, data from the DISSRM registry provides comparative survival outcomes between those undergoing AS, DI and PI. The salient data from each study are reported below.

Renal Cell Consortium of Canada

One of two reports by the RCCC on their prospective trial of AS was published in 2011 by Jewett, et al.[2] This study took place across 8 centers in Canada, with a total of 178 patients with 209 4 cm or smaller clinical stage T1aN0M0 SRM.[2] Each patient was either deemed unfit for surgery because of their comorbidities (although all had an estimated life expectancy of 2 or more years) or because they refused surgery.[2] Over a mean follow-up period of 28

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NOW APPROVED FOR ADVANCED RCC

LENVIMA® (lenvatinib) is indicated in combination with everolimus for the treatment of patients with advanced renal cell carcinoma (RCC) following one prior anti-angiogenic therapy

Indication

LENVIMA is indicated in combination with everolimus for the treatment of patients with advanced RCC following one prior anti-angiogenic therapy.

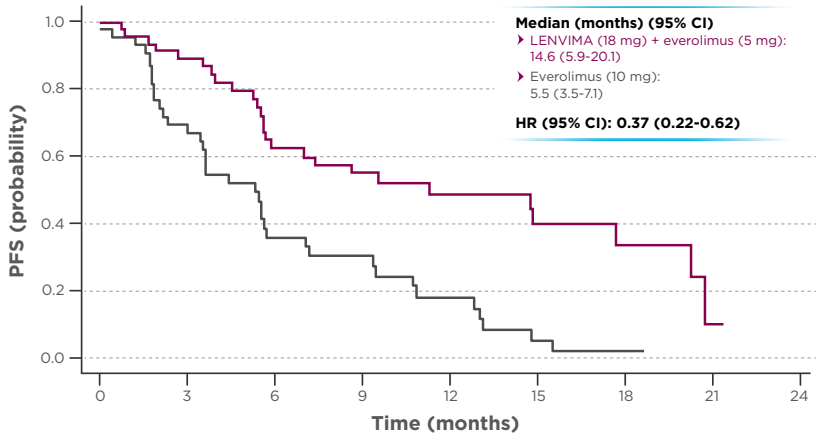
Important Safety Information

Warnings and Precautions

- Hypertension was reported in 42% of patients on LENVIMA + everolimus vs 10% with everolimus alone (13% vs 2% grade 3). Blood pressure should be controlled prior to treatment and monitored throughout. Withhold dose for grade 3 hypertension despite optimal antihypertensive therapy; resume at reduced dose when controlled at grade ≤2. Discontinue for life-threatening hypertension
- Cardiac dysfunction was reported in 10% of patients on LENVIMA + everolimus vs 6% with everolimus alone (3% vs 2% grade 3). Monitor for signs/symptoms of cardiac decompensation. Withhold for grade 3 cardiac dysfunction. Resume at reduced dose or discontinue based on severity and persistence of cardiac dysfunction. Discontinue for grade 4 cardiac dysfunction
- Arterial thromboembolic events were reported in 2% of patients on LENVIMA + everolimus vs 6% with everolimus alone (2% vs 4% grade ≥3). Discontinue following an arterial thrombotic event. The safety of resuming LENVIMA after an arterial thromboembolic event has not been established, and LENVIMA has not been studied in patients who have had an arterial thromboembolic event within the previous 6 months
- Across clinical studies in which 1,160 patients received LENVIMA monotherapy, hepatic failure (including fatal events) was reported in 3 patients and acute hepatitis in 1 patient. ALT and AST increases (grade ≥3) occurred in 3% of patients on LENVIMA + everolimus vs 2% and 0% with everolimus alone, respectively. Monitor liver function before initiation, then every 2 weeks for the first 2 months, and at least monthly thereafter during treatment. Withhold dose for liver impairment grade ≥3 until resolved to grade 0, 1, or baseline. Resume at reduced dose or discontinue based on severity/persistence of hepatotoxicity. Discontinue for hepatic failure
- Proteinuria was reported in 31% of patients on LENVIMA + everolimus vs 14% with everolimus alone (8% vs 2% grade 3). Monitor for proteinuria before and during treatment. Withhold dose for proteinuria ≥2 g/24 h. Resume at reduced dose when proteinuria is <2 g/24 h. Discontinue for nephrotic syndrome
- Diarrhea was reported in 81% of patients on LENVIMA + everolimus vs 34% with everolimus alone (19% vs 2% grade ≥3). Initiate prompt medical management for the development of diarrhea. Monitor for dehydration. Withhold dose for diarrhea grade ≥3. Resume at a reduced dose when diarrhea resolves to grade 1 or baseline. Discontinue for grade 4 diarrhea despite medical management
- Events of renal impairment were reported in 18% of patients on LENVIMA + everolimus vs 12% with everolimus alone (10% vs 2% grade ≥3). Withhold LENVIMA for grade 3 or 4 renal failure/impairment. Resume at reduced dose or discontinue, depending on severity/persistence of renal impairment. Active management of diarrhea and any other gastrointestinal (GI) symptoms should be initiated for grade 1 events
- Events of GI perforation, abscess, or fistula (grade ≥3) were reported in 2% of patients on LENVIMA + everolimus vs 0% with everolimus alone. Discontinue in patients who develop GI perforation or life-threatening fistula
- QTc interval increases >60 ms were reported in 11% of patients on LENVIMA + everolimus (6% >500 ms) vs 0% with everolimus alone. Monitor electrocardiograms in patients with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, or patients taking drugs known to prolong the QT interval. Monitor and correct electrolyte abnormalities in all patients. Withhold dose for QTc interval prolongation >500 ms. Resume at reduced dose when QTc prolongation resolves to baseline

MEANINGFUL RESULTS ACROSS 3 EFFICACY MEASURES[1]

Substantial improvement in progression-free survival (PFS)



Number of subjects at risk

LENVIMA + everolimus	51	41	27	23	16	10	5	1	0
Everolimus	50	29	15	11	7	3	1	0	

CI=confidence interval; HR=hazard ratio.

Study 205 randomized 153 patients with advanced or metastatic renal cell carcinoma who had previously received anti-angiogenic therapy 1:1:1 to LENVIMA 18 mg + everolimus 5 mg, LENVIMA 24 mg monotherapy, or everolimus 10 mg monotherapy. All medications were administered orally once daily. Patients were required to have histological confirmation of clear cell RCC and Eastern Cooperative Oncology Group performance status of 0 or 1. Patients were stratified by hemoglobin level (≤13 g/dL vs >13 g/dL for males and ≤11.5 g/dL vs >11.5 g/dL for females) and corrected serum calcium (≥10 mg/dL vs <10 mg/dL). The major efficacy outcome measure was PFS. Other efficacy outcome measures include objective response rate (ORR) and overall survival (OS).

*Twenty-one patients (41%) who received LENVIMA + everolimus progressed vs 35 patients (70%) who received everolimus. Death occurred in 5 patients (10%) who received LENVIMA + everolimus vs 2 patients (4%) who received everolimus.

†Analysis was conducted after 63% of deaths had occurred in the LENVIMA + everolimus arm and 74% of deaths had occurred in the everolimus arm.

- **14.6-month** (95% CI: 5.9-20.1) median PFS with LENVIMA + everolimus vs 5.5 months (95% CI: 3.5-7.1) with everolimus alone (HR [95% CI]: 0.37 [0.22-0.62])
  - 26 events (51%) occurred in the LENVIMA + everolimus arm vs 37 events (74%) in the everolimus arm*

Powerful response

- **37% confirmed ORR** (95% CI: 24%-52%) with LENVIMA + everolimus vs 6% with everolimus (95% CI: 1%-17%)
  - 2% of patients in the LENVIMA + everolimus arm achieved a complete response vs 0 patients in the everolimus arm
  - 35% of patients in the LENVIMA + everolimus arm achieved a partial response vs 6% of patients in the everolimus arm

Clinically meaningful OS benefit

- **25.5-month** (95% CI: 16.4-32.1) median OS with LENVIMA + everolimus vs 15.4 months (95% CI: 11.8-20.6) with everolimus alone (HR [95% CI]: 0.67 [0.42-1.08])†

Visit www.LenvimaAdvancedRCC.com for more information.

- Hypocalcemia (grade ≥3) was reported in 6% of patients on LENVIMA + everolimus vs 2% with everolimus alone. Monitor blood calcium levels at least monthly and replace calcium as necessary. Interrupt and adjust LENVIMA as necessary
- Across clinical studies in which 1,160 patients received LENVIMA monotherapy, reversible posterior leukoencephalopathy syndrome (RPLS) was reported in 4 patients. Withhold LENVIMA for RPLS until fully resolved. Resume at reduced dose or discontinue based on the severity and persistence of neurologic symptoms
- Hemorrhagic events occurred in 34% of patients on LENVIMA + everolimus vs 26% with everolimus alone (8% vs 2% grade ≥3). The most frequently reported hemorrhagic event was epistaxis (23% for LENVIMA + everolimus vs 24% with everolimus alone). There was 1 fatal cerebral hemorrhage case. Discontinuation due to hemorrhagic events occurred in 3% of patients on LENVIMA + everolimus. Consider the risk of severe or fatal hemorrhage associated with tumor invasion/infiltration of major blood vessels (eg, carotid artery). Withhold dose for grade 3 hemorrhage. Resume at reduced dose or discontinue based on severity/persistence of hemorrhage. Discontinue for grade 4 hemorrhage
- Grade 1 or 2 hypothyroidism occurred in 24% of patients on LENVIMA + everolimus vs 2% with everolimus alone. In patients with normal or low thyroid-stimulating hormone (TSH) at baseline, elevation of TSH was observed postbaseline in 60% of patients on LENVIMA + everolimus vs 3% with everolimus alone. Monitor thyroid function prior to treatment initiation and monthly thereafter. Treat hypothyroidism according to standard medical practice to maintain a euthyroid state
- LENVIMA can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with LENVIMA and for at least 2 weeks following completion of therapy

Adverse Reactions

- The most common adverse reactions observed in patients treated with LENVIMA + everolimus vs everolimus alone were diarrhea (81% vs 34%), fatigue (73% vs 40%), arthralgia/myalgia (55% vs 32%), decreased appetite (53% vs 18%), vomiting (48% vs 12%), nausea (45% vs 16%), stomatitis/oral inflammation (44% vs 50%), hypertension/increased blood pressure (42% vs 10%), peripheral edema (42% vs 20%), cough (37% vs 30%), abdominal pain (37% vs 8%), dyspnea/exertional dyspnea (35% vs 28%), rash (35% vs 40%), weight decreased (34% vs 8%), hemorrhagic events (32% vs 26%), and proteinuria/urine protein present (31% vs 14%)
- Adverse reactions led to dose reductions or interruption in 89% of patients receiving LENVIMA + everolimus and in 54% of patients receiving everolimus. The most common adverse reactions (≥5%) resulting in dose reductions in the LENVIMA + everolimus–treated group were diarrhea (21%), fatigue (8%), thrombocytopenia (6%), vomiting (6%), nausea (5%), and proteinuria (5%). Treatment discontinuation due to an adverse reaction occurred in 29% of patients in the LENVIMA + everolimus–treated group and in 12% of patients in the everolimus-treated group

Use in Specific Populations

- Because of the potential for serious adverse reactions in nursing infants, advise women to discontinue breastfeeding during treatment
- LENVIMA may result in reduced fertility in females of reproductive potential and may result in damage to male reproductive tissues, leading to reduced fertility of unknown duration

Please see accompanying brief summary of full Prescribing Information.

LENVIMA® (lenvatinib) capsules 10 mg and 4 mg
RESPONSE THAT MATTERS

Reference: 1. LENVIMA [package insert]. Woodcliff Lake, NJ: Eisai Inc.; 2016.

LENVIMA® (lenvatinib) BRIEF SUMMARY –
See package insert for full prescribing information.

1 INDICATIONS AND USAGE

1.1 Differentiated Thyroid Cancer

LENVIMA is indicated for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory DTC.

1.2 Renal Cell Carcinoma

LENVIMA is indicated in combination with everolimus for the treatment of patients with advanced RCC following one prior anti-angiogenic therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose for DTC

The recommended daily dose of LENVIMA is 24 mg (two 10 mg capsules and one 4 mg capsule) orally taken once daily with or without food. Continue LENVIMA until disease progression or until unacceptable toxicity.

Take LENVIMA at the same time each day. If a dose is missed and cannot be taken within 12 hours, skip that dose and take the next dose at the usual time of administration.

2.2 Recommended Dose for RCC

The recommended daily dose of LENVIMA is 18 mg (one 10 mg capsule and two 4 mg capsules) in combination with 5 mg everolimus orally taken once daily with or without food. Continue LENVIMA plus everolimus until disease progression or until unacceptable toxicity.

Take LENVIMA and everolimus at the same time each day. If a dose is missed and cannot be taken within 12 hours, skip that dose and take the next dose at the usual time of administration.

2.3 Administration Instructions

LENVIMA capsules should be swallowed whole. Alternatively, the capsules can be dissolved in a small glass of liquid. Measure 1 tablespoon of water or apple juice and put the capsules into the liquid without breaking or crushing them. Leave the capsules in the liquid for at least 10 minutes. Stir for at least 3 minutes. Drink the mixture. After drinking, add the same amount (1 tablespoon) of water or apple juice to the glass. Swirl the contents a few times and swallow the additional liquid.

2.4 Dose Modifications for DTC and RCC

Table 1: Adverse Reactions Requiring Dose Modification of LENVIMA in DTC and RCC

Adverse Reaction	CTCAE Grade	Action	Dose Reduce and Resume LENVIMA
Hypertension	Grade 3[1]	Hold	Resolves to Grade 0, 1, or 2
	Grade 4	Discontinue	Do Not Resume
Cardiac Dysfunction	Grade 3	Hold	Resolves to Grade 0, 1, or baseline
	Grade 4	Discontinue	Do Not Resume
Arterial Thrombotic Event	Any Grade	Discontinue	Do Not Resume
Hepatotoxicity	Grade 3 or 4	Hold OR Discontinue	Consider resuming at reduced dose if resolves to Grade 0-1 or baseline
Hepatic Failure	Grade 3 or 4	Discontinue	Do Not Resume
Proteinuria	Greater than or equal to 2 gm/24 hours	Hold	Resolves to less than 2 gm/24 hours
Nephrotic Syndrome	-------	Discontinue	Do Not Resume
Nausea, Vomiting, and Diarrhea[2]	Grade 3	Hold	Resolves to Grade 0, 1, or baseline
Vomiting and Diarrhea[2]	Grade 4	Discontinue	Do Not Resume
Renal Failure or Impairment	Grade 3 or 4	Hold OR Discontinue	Consider resuming at reduced dose if resolves to Grade 0-1 or baseline
GI Perforation	Any Grade	Discontinue	Do Not Resume
Fistula	Grade 3 or 4	Discontinue	Do Not Resume
QTc Prolongation	Greater than 500 ms	Hold	Resolves to less than 480 ms or baseline
RPLS	Any Grade	Hold OR Discontinue	Consider resuming at reduced dose if resolves to Grade 0 to 1
Hemorrhage	Grade 3	Hold	Resolves to Grade 0 to 1
	Grade 4	Discontinue	Do Not Resume

[1] Grade 3 despite optimal anti-hypertensive therapy
[2] Initiate prompt medical management for nausea, vomiting or diarrhea. Permanently discontinue for Grade 4 vomiting and diarrhea despite medical management.

Manage other adverse reactions according to the instructions in Table 2 for DTC or Table 3 for RCC.

Recommendations for Dose Modifications in DTC

Table 2: Dose Modifications for LENVIMA for Persistent and Intolerable Grade 2 or Grade 3 Adverse Reactions or Grade 4 Laboratory Abnormalities in DTC[a]

Adverse Reaction	Modification	Adjusted Dose[b]
First occurrence	Interrupt until resolved to Grade 0-1 or baseline	20 mg (two 10 mg capsules) orally once daily
Second occurrence[c]	Interrupt until resolved to Grade 0-1 or baseline	14 mg (one 10 mg capsule plus one 4 mg capsule) orally once daily
Third occurrence[c]	Interrupt until resolved to Grade 0-1 or baseline	10 mg (one 10 mg capsule) orally once daily

[a] Initiate medical management for nausea, vomiting, or diarrhea prior to interruption or dose reduction of LENVIMA
[b] Reduce dose in succession based on the previous dose level (24 mg, 20 mg, or 14 mg per day)
[c] Refers to the same or a different adverse reaction that requires dose modification

Severe Renal or Hepatic Impairment in DTC

For patients with DTC, the recommended dose of LENVIMA is 14 mg taken orally once daily in patients with severe renal impairment (creatinine clearance [CLcr] less than 30 mL/min calculated by the Cockcroft-Gault equation) or severe hepatic impairment (Child-Pugh C).

Recommendations for Dose Modifications in RCC

Table 3: Dose Modifications for LENVIMA for Persistent and Intolerable Grade 2 or Grade 3 Adverse Reactions or Grade 4 Laboratory Abnormalities in RCC[a]

Adverse Reaction	Modification	Adjusted Dose[b]
First occurrence	Interrupt until resolved to Grade 0-1 or baseline	14 mg (one 10 mg capsules plus one 4 mg capsule) orally once daily
Second occurrence[c]	Interrupt until resolved to Grade 0-1 or baseline	10 mg (one 10 mg capsule) orally once daily
Third occurrence[c]	Interrupt until resolved to Grade 0-1 or baseline	8 mg (two 4 mg capsules) orally once daily

[a] Initiate medical management for nausea, vomiting, or diarrhea prior to interruption or dose reduction of LENVIMA
[b] Reduce dose in succession based on the previous dose level (18 mg, 14 mg, 10 mg, or 8 mg per day)
[c] Refers to the same or a different adverse reaction that requires dose modification

Recommendations for Dose Modification of Everolimus in RCC

Review the Full Prescribing Information for everolimus for recommended dose modifications. For toxicities thought to be related to everolimus alone, discontinue, interrupt, or use alternate day dosing. For toxicities thought to be related to both LENVIMA and everolimus, first reduce LENVIMA and then everolimus.

Severe Renal or Hepatic Impairment in RCC

For patients with RCC, the recommended dose of LENVIMA is 10 mg taken orally once daily in patients with severe renal impairment (CLcr less than 30 mL/min calculated by the Cockcroft-Gault equation) or severe hepatic impairment (Child-Pugh C).

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hypertension

In Study 1 in DTC, hypertension was reported in 73% of LENVIMA-treated patients and 16% of patients in the placebo group. The median time to onset of new or worsening hypertension was 16 days for LENVIMA-treated patients. The incidence of Grade 3 hypertension was 44% as compared to 4% for placebo, and the incidence of Grade 4 hypertension was less than 1% in LENVIMA-treated patients and none in the placebo group.

In Study 2 in RCC, hypertension was reported in 42% of patients in the LENVIMA + everolimus-treated group and 10% of patients in the everolimus-treated group. The median time to onset of new or worsening hypertension was 35 days for LENVIMA + everolimus-treated patients. The incidence of Grade 3 hypertension was 13% in the LENVIMA + everolimus-treated group as compared to 2% in the everolimus-treated group. Systolic blood pressure ≥ 160mmHg occurred in 29% and 21% of patients had a diastolic blood pressure ≥100 in the LENVIMA + everolimus-treated group.

Control blood pressure prior to treatment with LENVIMA. Monitor blood pressure after 1 week, then every 2 weeks for the first 2 months, and then at least monthly thereafter during treatment with LENVIMA. Withhold LENVIMA for Grade 3 hypertension despite optimal antihypertensive therapy; resume at a reduced dose when hypertension is controlled at less than or equal to Grade 2. Discontinue LENVIMA for life-threatening hypertension.

5.2 Cardiac Dysfunction

In Study 1 in DTC, cardiac dysfunction, defined as decreased left or right ventricular function, cardiac failure, or pulmonary edema, was reported in 7% of LENVIMA-treated patients (2% Grade 3 or greater) and 2% (no Grade 3 or greater) of patients in the placebo group. The majority of these cases in LENVIMA-treated patients (14 of 17 cases) were based on findings of decreased ejection fraction as assessed by echocardiography. Six of 261 (2%) LENVIMA-treated patients in Study 1 had greater than 20% reduction in ejection fraction as measured by echocardiography compared to no patients who received placebo.

In Study 2 in RCC, decreased ejection fraction and cardiac failure were reported in 10% of patients in the LENVIMA + everolimus-treated group and 6% of patients in the everolimus-treated group. Grade 3 events occurred in 3% of LENVIMA + everolimus-treated patients and 2% of everolimus-treated patients. In the LENVIMA + everolimus-treated group there were two patients with a Grade 2 to 4 decrease in LVEF as assessed by MUGA.

Monitor patients for clinical symptoms or signs of cardiac decompensation. Withhold LENVIMA for development of Grade 3 cardiac dysfunction until improved to Grade 0 or 1 or baseline. Either resume at a reduced dose or discontinue LENVIMA depending on the severity and persistence of cardiac dysfunction. Discontinue LENVIMA for Grade 4 cardiac dysfunction.

5.3 Arterial Thromboembolic Events

In Study 1 in DTC, arterial thromboembolic events were reported in 5% of LENVIMA-treated patients and 2% of patients in the placebo group. The incidence of arterial thromboembolic events of Grade 3 or greater was 3% in LENVIMA-treated patients and 1% in the placebo group.

In Study 2 in RCC, 2% of patients in the LENVIMA + everolimus-treated group and 6% of patients in the everolimus-treated group had arterial thromboembolic events reported. The incidence of arterial thromboembolic events of Grade 3 or greater was 2% with LENVIMA + everolimus-treated patients and 4% in the everolimus-treated group.

Discontinue LENVIMA following an arterial thrombotic event. The safety of resuming LENVIMA after an arterial thromboembolic event has not been established and LENVIMA has not been studied in patients who have had an arterial thromboembolic event within the previous 6 months.

5.4 Hepatotoxicity

Across clinical studies in which 1160 patients received LENVIMA monotherapy, hepatic failure (including fatal events) was reported in 3 patients and acute hepatitis was reported in 1 patient.

In Study 1 in DTC, 4% of LENVIMA-treated patients experienced an increase in alanine aminotransferase (ALT) and 5% experienced an increase in aspartate aminotransferase (AST) that was Grade 3 or greater. No patients in the placebo group experienced Grade 3 or greater increases in ALT or AST.

The incidence of ALT and AST elevation was similar in Study 2 in RCC. In Study 2, 3% of LENVIMA + everolimus-treated patients experienced an increase in ALT and 3% experienced an increase in AST that was Grade 3 or greater. Two percent of patients in the everolimus-treated group experienced an increase in ALT and none experienced an increase in AST that was Grade 3 or greater.

Monitor liver function before initiation of LENVIMA, then every 2 weeks for the first 2 months, and at least monthly thereafter during treatment. Withhold LENVIMA for the development of Grade 3 or greater liver impairment until resolved to Grade 0 to 1 or baseline. Either resume at a reduced dose or discontinue LENVIMA depending on the severity and persistence of hepatotoxicity. Discontinue LENVIMA for hepatic failure.

5.5 Proteinuria

In Study 1 in DTC, proteinuria was reported in 34% of LENVIMA-treated patients and 3% of patients in the placebo group. The incidence of Grade 3 proteinuria in LENVIMA-treated patients was 11% compared to none in the placebo group.

In Study 2 in RCC, proteinuria was reported in 31% of patients in the LENVIMA + everolimus-treated group and 14% of patients in the everolimus-treated group. The incidence of Grade 3 proteinuria in LENVIMA + everolimus-treated patients was 8% compared to 2% in everolimus-treated patients.

Monitor for proteinuria before initiation of, and periodically throughout, treatment. If urine dipstick proteinuria greater than or equal to 2+ is detected, obtain a 24 hour urine protein. Withhold LENVIMA for ≥2 grams of proteinuria/24 hours and resume at a reduced dose when proteinuria is <2 gm/24 hours. Discontinue LENVIMA for nephrotic syndrome.

5.6 Diarrhea

In Study 2 in RCC, diarrhea was reported in 81% of LENVIMA + everolimus-treated patients and 34% of everolimus-treated patients. Grade 3 or 4 events occurred in 21% of LENVIMA + everolimus-treated patients and 2% of everolimus-treated patients. Diarrhea was the most frequent cause of dose interruption/reduction and recurred despite dose reduction. Diarrhea resulted in discontinuation in one patient.

Initiate prompt medical management for the development of diarrhea. Monitor for dehydration. Interrupt LENVIMA for Grade 3 or 4 diarrhea. For Grade 3 diarrhea, resume at a reduced dose of LENVIMA when diarrhea resolves to Grade 1 or baseline. Permanently discontinue LENVIMA for Grade 4 diarrhea despite medical management.

5.7 Renal Failure and Impairment

In Study 1 in DTC, events of renal impairment were reported in 14% of LENVIMA-treated patients compared to 2% of patients in the placebo group. The incidence of Grade 3 or greater renal failure or impairment was 3% in LENVIMA-treated patients and 1% in the placebo group.

In Study 2 in RCC, renal impairment was reported in 18% of LENVIMA + everolimus-treated group and 12% in the everolimus-treated group. The incidence of Grade 3 or greater renal failure or impairment was 10% in the LENVIMA + everolimus-treated group and 2% in the everolimus-treated group.

One risk factor for severe renal impairment in LENVIMA-treated patients was dehydration/hypovolemia due to diarrhea and vomiting. Active management of diarrhea and any other gastrointestinal symptoms should be initiated for Grade 1 events.

Withhold LENVIMA for development of Grade 3 or 4 renal failure/impairment until resolved to Grade 0 to 1 or baseline. Either resume at a reduced dose or discontinue LENVIMA depending on the severity and persistence of renal impairment.

5.8 Gastrointestinal Perforation and Fistula Formation

In Study 1 in DTC, events of gastrointestinal perforation or fistula were reported in 2% of LENVIMA-treated patients and 0.8% of patients in the placebo group.

In Study 2 in RCC, Grade 3 or greater gastrointestinal perforation, abscess or fistula was reported in 2% of patients in the LENVIMA + everolimus-treated group and no patients in the everolimus-treated group. The events resolved in all patients.

Discontinue LENVIMA in patients who develop gastrointestinal perforation or life-threatening fistula.

5.9 QT Interval Prolongation

In Study 1 in DTC, QT/QTc interval prolongation was reported in 9% of LENVIMA-treated patients and 2% of patients in the placebo group. The incidence of QT interval prolongation of greater than 500 ms was 2% in LENVIMA-treated patients compared to no reports in the placebo group.

In Study 2 in RCC, QTc interval increases greater than 60 ms were reported in 11% of patients in the LENVIMA + everolimus-treated group. The incidence of QTc interval greater than 500 ms was 6% in the LENVIMA + everolimus-treated group. No reports of QTc interval prolongation greater than 500 ms or increase greater than 60 ms occurred in the everolimus-treated group.

Monitor and correct electrolyte abnormalities in all patients. Monitor electrocardiograms in patients with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, or those who are taking drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics. Withhold LENVIMA for the development of QTc interval prolongation greater than 500 ms. Resume LENVIMA at a reduced dose when QTc prolongation resolves to baseline.

5.10 Hypocalcemia

In Study 1 in DTC, 9% of LENVIMA-treated patients experienced Grade 3 or greater hypocalcemia compared to 2% in the placebo group. In most cases hypocalcemia responded to replacement and dose interruption/dose reduction.

In Study 2 in RCC, 6% of patients in the LENVIMA + everolimus-treated group and 2% of patients in the everolimus-treated group experienced Grade 3 or greater hypocalcemia. No patients discontinued due to hypocalcemia.

Monitor blood calcium levels at least monthly and replace calcium as necessary during LENVIMA treatment. Interrupt and adjust LENVIMA dosing as necessary depending on severity, presence of ECG changes, and persistence of hypocalcemia.

5.11 Reversible Posterior Leukoencephalopathy Syndrome

Across clinical studies in which 1160 patients received LENVIMA monotherapy, there were 4 reported events of reversible posterior leukoencephalopathy syndrome (RPLS). Confirm the diagnosis of RPLS with MRI. Withhold for RPLS until fully resolved. Upon resolution, resume at a reduced dose or discontinue LENVIMA depending on the severity and persistence of neurologic symptoms.

5.12 Hemorrhagic Events

Across clinical studies in which 1160 patients received LENVIMA monotherapy, Grade 3 or greater hemorrhage was reported in 2% of patients.

In Study 1 in DTC, hemorrhagic events occurred in 35% of LENVIMA-treated patients and in 18% of the placebo group. However, the incidence of Grade 3 to 5 hemorrhage was similar between arms at 2% and 3%, respectively. There was 1 case of fatal intracranial hemorrhage among 16 patients who received LENVIMA and had CNS metastases at baseline. The most frequently reported hemorrhagic event was epistaxis (11% Grade 1 and 1% Grade 2). Discontinuation due to hemorrhagic events occurred in 1% of LENVIMA-treated patients.

In Study 2 in RCC, hemorrhagic events occurred in 34% of patients in the LENVIMA + everolimus-treated group and 26% of patients in the everolimus-treated group. The most frequently reported hemorrhagic event was epistaxis (LENVIMA + everolimus 23% and everolimus 24%). Grade 3 or greater events occurred in 8% of LENVIMA + everolimus-treated patients and in 2% of everolimus-treated patients. In the LENVIMA + everolimus-treated patients, this included one fatal cerebral hemorrhage. Discontinuation due to a hemorrhagic event occurred in 3% of patients in the LENVIMA + everolimus-treated group.

Serious tumor related bleeds, including fatal hemorrhagic events in LENVIMA-treated patients, have occurred in clinical trials and been reported in post-marketing experience. In post-marketing surveillance, serious and fatal carotid artery hemorrhages were seen more frequently in patients with anaplastic thyroid carcinoma (ATC) than in other tumor types. The safety and effectiveness of LENVIMA in patients with ATC have not been demonstrated in clinical trials.

Consider the risk of severe or fatal hemorrhage associated with tumor invasion/infiltration of major blood vessels (e.g. carotid artery). Withhold LENVIMA for the development of Grade 3 hemorrhage until resolved to Grade 0 to 1. Either resume at a reduced dose or discontinue LENVIMA depending on the severity and persistence of hemorrhage. Discontinue LENVIMA in patients who experience Grade 4 hemorrhage.

5.13 Impairment of Thyroid Stimulating Hormone Suppression/Thyroid Dysfunction

LENVIMA impairs exogenous thyroid suppression. In Study 1 in DTC, 88% of all patients had a baseline thyroid stimulating hormone (TSH) level less than or equal to 0.5 mU/L. In those patients with a normal TSH at baseline, elevation of TSH level above 0.5 mU/L was observed post baseline in 57% of LENVIMA-treated patients as compared with 14% of patients receiving placebo.

In Study 2 in RCC, Grade 1 or 2 hypothyroidism occurred in 24% of patients in the LENVIMA + everolimus-treated group and 2% of patients in the everolimus-treated group. In those patients with a normal or low TSH at baseline, an elevation of TSH was observed post baseline in 60 % of LENVIMA + everolimus-treated patients as compared with 3% of patients receiving everolimus monotherapy.

Monitor thyroid function before initiation of, and at least monthly throughout, treatment with LENVIMA. Treat hypothyroidism according to standard medical practice to maintain a euthyroid state.

5.14 Embryofetal Toxicity

Based on its mechanism of action and data from animal reproduction studies, LENVIMA can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, oral administration of lenvatinib during organogenesis at doses below the recommended human dose resulted in embryotoxicity, fetotoxicity, and teratogenicity in rats and rabbits. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with LENVIMA and for at least 2 weeks following completion of therapy.

6 ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in the label:

- Hypertension
- Cardiac Dysfunction
- Arterial Thromboembolic Events
- Hepatotoxicity
- Proteinuria
- Diarrhea
- Renal Failure and Impairment
- Gastrointestinal Perforation and Fistula Formation
- QT Interval Prolongation
- Hypocalcemia
- Reversible Posterior Leukoencephalopathy Syndrome
- Hemorrhagic Events
- Impairment of Thyroid Stimulating Hormone Suppression/Thyroid Dysfunction

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.

The data in the Warnings and Precautions section reflect exposure to LENVIMA as a single agent in 261 DTC patients (Study 1) and LENVIMA + everolimus in 62 RCC patients (Study 2). Safety data obtained in 1160 patients with advanced solid tumors who received LENVIMA as a single agent across multiple clinical studies was used to further characterize the risks of serious adverse reactions. In the entire single agent population, the median age was 60 years (range 21-89 years), the dose range was 0.2 mg to 32 mg, and the median duration of exposure was 5.5 months.

Differentiated Thyroid Cancer

The safety data described below are derived from Study 1 which randomized (2:1) patients with radioactive iodine-refractory differentiated thyroid cancer (RAI-refractory DTC) to LENVIMA (n=261) or placebo (n=131). The median treatment duration was 16.1 months for LENVIMA and 3.9 months for placebo. Among 261 patients who received LENVIMA in Study 1, median age was 64 years, 52% were women, 80% were White, 18% were Asian, and 2% were Black; 4% identified themselves as having Hispanic or Latino ethnicity.

In Study 1, the most common adverse reactions observed in LENVIMA-treated patients (greater than or equal to 30%) were, in order of decreasing frequency, hypertension, fatigue, diarrhea, arthralgia/myalgia, decreased appetite, weight decreased, nausea, stomatitis, headache, vomiting, proteinuria, palmar-plantar erythrodysesthesia (PPE) syndrome, abdominal pain, and dysphonia. The most common serious adverse reactions (at least 2%) were pneumonia (4%), hypertension (3%), and dehydration (3%).

Adverse reactions led to dose reductions in 68% of patients receiving LENVIMA and 5% of patients receiving placebo; 18% of patients discontinued LENVIMA and 5% discontinued placebo for adverse reactions. The most common adverse reactions (at least 10%) resulting in dose reductions of LENVIMA were hypertension (13%), proteinuria (11%), decreased appetite (10%), and diarrhea (10%); the most common adverse reactions (at least 1%) resulting in discontinuation of LENVIMA were hypertension (1%) and asthenia (1%).

Table 4 presents the percentage of patients in Study 1 experiencing adverse reactions at a higher rate in LENVIMA-treated patients than patients receiving placebo in the double-blind phase of the DTC study.

Table 4: Adverse Reactions Occurring in Patients with a Between-Group Difference of Greater than or Equal to 5% in All Grades or Greater than or Equal to 2% in Grades 3 and 4

Adverse Reaction	LENVIMA 24 mg N=261		Placebo N=131	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Vascular Disorders				
Hypertension[a]	73	44	16	4
Hypotension	9	2	2	0
Gastrointestinal Disorders				
Diarrhea	67	9	17	0
Nausea	47	2	25	1
Stomatitis[b]	41	5	8	0
Vomiting	36	2	15	0
Abdominal pain[c]	31	2	11	1
Constipation	29	0.4	15	1
Oral pain[d]	25	1	2	0
Dry mouth	17	0.4	8	0
Dyspepsia	13	0.4	4	0
General Disorders and Administration Site Conditions				
Fatigue[e]	67	11	35	4
Edema peripheral	21	0.4	8	0
Musculoskeletal and Connective Tissue Disorders				
Arthralgia/Myalgia[f]	62	5	28	3
Metabolism and Nutrition Disorders				
Weight decreased	51	13	15	1
Decreased appetite	54	7	18	1
Dehydration	9	2	2	1
Nervous System Disorders				
Headache	38	3	11	1
Dysgeusia	18	0	3	0
Dizziness	15	0.4	9	0
Renal and Urinary Disorders				
Proteinuria	34	11	3	0
Skin and Subcutaneous Tissue Disorders				
Palmar-plantar erythrodysesthesia	32	3	1	0
Rash[g]	21	0.4	3	0
Alopecia	12	0	5	0
Hyperkeratosis	7	0	2	0
Respiratory, Thoracic and Mediastinal Disorders				
Dysphonia	31	1	5	0
Cough	24	0	18	0
Epistaxis	12	0	1	0
Psychiatric Disorders				
Insomnia	12	0	3	0
Infections and Infestations				
Dental and oral infections[h]	10	1	1	0
Urinary tract infection	11	1	5	0
Cardiac Disorders				
Electrocardiogram QT prolonged	9	2	2	0

[a] Includes hypertension, hypertensive crisis, increased blood pressure diastolic, and increased blood pressure
[b] Includes aphthous stomatitis, stomatitis, glossitis, mouth ulceration, and mucosal inflammation
[c] Includes abdominal discomfort, abdominal pain, lower abdominal pain, upper abdominal pain, abdominal tenderness, epigastric discomfort, and gastrointestinal pain
[d] Includes oral pain, glossodynia, and oropharyngeal pain
[e] Includes asthenia, fatigue, and malaise
[f] Includes musculoskeletal pain, back pain, pain in extremity, arthralgia, and myalgia
[g] Includes macular rash, maculo-papular rash, generalized rash, and rash
[h] Includes gingivitis, oral infection, parotitis, pericoronitis, periodontitis, sialoadenitis, tooth abscess, and tooth infection

A clinically important adverse reaction occurring more frequently in LENVIMA-treated patients than patients receiving placebo, but with an incidence of less than 5% was pulmonary embolism (3%, including fatal reports vs 2%, respectively).

Table 5: Laboratory Abnormalities with a Difference of at Least ≥2% in Grade 3 - 4 Events and at a Higher Incidence in LENVIMA-Treated Patients[a]

Laboratory Abnormality	LENVIMA 24 mg N=258[b]	Placebo N=131[b]
	Grades 3-4 (%)	Grades 3-4 (%)
Chemistry		
Creatinine increased	3	0
Alanine aminotransferase (ALT) increased	4	0
Aspartate aminotransferase (AST) increased	5	0
Hypocalcemia	9	2
Hypokalemia	6	1
Lipase increased	4	1
Hematology		
Platelet count decreased	2	0

[a] With at least 1 grade increase from baseline
[b] Subject with at least 1 post baseline laboratory value

In addition the following laboratory abnormalities (all Grades) occurred in greater than 5% of LENVIMA-treated patients and at a rate that was two-fold or higher than in patients who received placebo: hypoalbuminemia, increased alkaline phosphatase, hypomagnesemia, hypoglycemia, hyperbilirubinemia, hypercalcemia, hypercholesterolemia, increased serum amylase, and hyperkalemia.

Renal Cell Carcinoma

The data described below are derived from Study 2 which randomized (1:1:1) patients with unresectable advanced or metastatic renal cell carcinoma (RCC) to LENVIMA 18 mg + everolimus 5 mg (n=51), LENVIMA 24 mg (n=52), or everolimus 10 mg (n=50) once daily. This data also includes patients on the dose escalation portion of the study who received LENVIMA 18 mg + everolimus 5 mg (n=11). The median treatment duration was 8.1 months for LENVIMA + everolimus and 4.1 months for everolimus. Among 62 patients who received LENVIMA + everolimus in Study 2, the median age was 61 years, 71% were men, and 98% were White.

The most common adverse reactions observed in the LENVIMA + everolimus-treated group (> 30%) were, in order of decreasing frequency, diarrhea, fatigue, arthralgia/myalgia, decreased appetite, vomiting, nausea, stomatitis/oral inflammation, hypertension, peripheral edema, cough, abdominal pain, dyspnea, rash, weight decreased, hemorrhagic events, and proteinuria. The most common serious adverse reactions (≥ 5%) were renal failure (11%), dehydration (10%), anemia (6%), thrombocytopenia (5%), diarrhea (5%), vomiting (5%), and dyspnea (5%).

Adverse reactions led to dose reductions or interruption in 89% of patients receiving LENVIMA + everolimus and 54% in patients receiving everolimus. The most common adverse reactions (≥ 5%) resulting in dose reductions in the LENVIMA + everolimus-treated group were diarrhea (21%), fatigue (8%), thrombocytopenia (6%), vomiting (6%), nausea (5%), and proteinuria (5%).

Treatment discontinuation due to an adverse reaction occurred in 29% of patients in the LENVIMA + everolimus-treated group and 12% of patients in the everolimus-treated group.

Table 6 presents the adverse reactions in > 15% of patients in the LENVIMA + everolimus arm.

Table 6: Grade 1-4 Adverse Reactions in > 15% of Patients in the LENVIMA + Everolimus Arm

System Organ Class Preferred Term	LENVIMA 18 mg + Everolimus 5 mg (N=62)		Everolimus 10 mg (N=50)	
	Grade 1-4 (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Endocrine Disorders				
Hypothyroidism	24	0	2	0
Gastrointestinal Disorders				
Constipation	16	0	18	0
Diarrhea	81	19	34	2
Dyspepsia/Gastro-esophageal reflux	21	0	12	0
Abdominal pain[a]	37	3	8	0
Nausea	45	5	16	0
Oral pain[b]	23	2	4	0
Stomatitis/Oral inflammation[c]	44	2	50	4
Vomiting	48	7	12	0
General Disorders and Administration Site Conditions				
Fatigue[d]	73	18	40	2
Peripheral edema	42	2	20	0
Pyrexia/Increased body temperature	21	2	10	2
Investigations				
Weight decreased	34	3	8	0
Metabolism and Nutrition Disorders				
Decreased appetite	53	5	18	0
Musculoskeletal and Connective Tissue Disorders				
Arthralgia/Myalgia[e]	55	5	32	0
Musculoskeletal chest pain	18	2	4	0
Nervous System Disorders				
Headache	19	2	10	2
Psychiatric Disorders				
Insomnia	16	2	2	0
Renal and Urinary Disorders				
Proteinuria/Urine protein present	31	8	14	2
Renal failure event[f]	18	10	12	2
Respiratory, Thoracic and Mediastinal Disorders				
Cough	37	0	30	0
Dysphonia	18	0	4	0
Dyspnea/Exertional dyspnea	35	5	28	8
Skin and Subcutaneous Tissue Disorders				
Rash[g]	35	0	40	0
Vascular Disorders				
Hemorrhagic events[h]	32	6	26	2
Hypertension/Increased blood pressure	42	13	10	2

[a] Includes abdominal discomfort, gastrointestinal pain, lower abdominal pain, and upper abdominal pain
[b] Includes gingival pain, glossodynia, and oropharyngeal pain
[c] Includes aphthous stomatitis, gingival inflammation, glossitis, and mouth ulceration
[d] Includes asthenia, fatigue, lethargy and malaise
[e] Includes arthralgia, back pain, extremity pain, musculoskeletal pain, and myalgia
[f] Includes blood creatinine increased, blood urea increased, creatinine renal clearance decreased, nephropathy toxic, renal failure, renal failure acute, and renal impairment,
[g] Includes erythema, erythematous rash, genital rash, macular rash, maculo-papular rash, , papular rash, pruritic rash, pustular rash, and septic rash
[h] Includes hemorrhagic diarrhea, epistaxis, gastric hemorrhage, hemarthrosis, hematoma, hematuria, hemoptysis, lip hemorrhage, renal hematoma, and scrotal hematocele

Table 7: Grade 3-4 Laboratory Abnormalities in ≥ 3% of Patients in the LENVIMA + Everolimus Arm[a,b]

Laboratory Abnormality	LENVIMA 18 mg + Everolimus 5 mg N=62 Grades 3-4 (%)	Everolimus 10 mg N=50 Grades 3-4 (%)
Chemistry		
Aspartate aminotransferase (AST) increased	3	0
Alanine aminotransferase (ALT) increased	3	2
Alkaline phosphatase increased	3	0
Hyperkalemia	6	2
Hypokalemia	6	2
Hyponatremia	11	6
Hypocalcemia	6	2
Hypophosphatemia	11	6
Hyperglycemia	3	16
Hypertriglyceridemia	18	18
Elevated cholesterol	11	0
Creatine kinase increased	3	4
Lipase increased	13	12
Hematology		
Hemoglobin decreased	8	16
Platelet count decreased	5	0
Lymphocyte count decreased	10	20

[a] With at least 1 grade increase from baseline
[b] Subject with at least 1 post baseline laboratory value

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on Lenvatinib

No dose adjustment of LENVIMA is recommended when co-administered with CYP3A, P-glycoprotein (P-gp), and breast cancer resistance protein (BCRP) inhibitors and CYP3A and P-gp inducers.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action and data from animal reproduction studies, LENVIMA can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, oral administration of lenvatinib during organogenesis at doses below the recommended human dose resulted in embryotoxicity, fetotoxicity, and teratogenicity in rats and rabbits. There are no available human data informing the drug-associated risk. Advise pregnant women of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown; however, the background risk in the U.S. general population of major birth defects is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies.

Data

Animal Data

In an embryofetal development study, daily oral administration of lenvatinib mesylate at doses greater than or equal to 0.3 mg/kg [approximately 0.14 times the recommended human dose based on body surface area (BSA)] to pregnant rats during organogenesis resulted in dose-related decreases in mean fetal body weight, delayed fetal ossifications, and dose-related increases in fetal external (parietal edema and tail abnormalities), visceral, and skeletal anomalies. Greater than 80% postimplantation loss was observed at 1.0 mg/kg/day (approximately 0.5 times the recommended human dose based on BSA).

Daily oral administration of lenvatinib mesylate to pregnant rabbits during organogenesis resulted in fetal external (short tail), visceral (retroesophageal subclavian artery), and skeletal anomalies at doses greater than or equal to 0.03 mg/kg (approximately 0.03 times the human dose of 24 mg based on body surface area). At the 0.03 mg/kg dose, increased post-implantation loss, including 1 fetal death, was also observed. Lenvatinib was abortifacient in rabbits, resulting in late abortions in approximately one-third of the rabbits treated at a dose level of 0.5 mg/kg/day (approximately 0.5 times the recommended clinical dose of 24 mg based on BSA).

8.2 Lactation

Risk Summary

It is not known whether LENVIMA is present in human milk. However, lenvatinib and its metabolites are excreted in rat milk at concentrations higher than in maternal plasma. Because of the potential for serious adverse reactions in nursing infants from LENVIMA, advise women to discontinue breastfeeding during treatment with LENVIMA.

Data

Animal Data

Following administration of radiolabeled lenvatinib to lactating Sprague Dawley rats, lenvatinib-related radioactivity was approximately 2 times higher (based on AUC) in milk compared to maternal plasma.

8.3 Females and Males of Reproductive Potential

Contraception

Based on its mechanism of action, LENVIMA can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with LENVIMA and for at least 2 weeks following completion of therapy.

Infertility

Females

LENVIMA may result in reduced fertility in females of reproductive potential.

Males

LENVIMA may result in damage to male reproductive tissues leading to reduced fertility of unknown duration.

8.4 Pediatric Use

The safety and effectiveness of LENVIMA in pediatric patients have not been established.

Juvenile Animal Data

Daily oral administration of lenvatinib mesylate to juvenile rats for 8 weeks starting on postnatal day 21 (approximately equal to a human pediatric age of 2 years) resulted in growth retardation (decreased body weight gain, decreased food consumption, and decreases in the width and/or length of the femur and tibia) and secondary delays in physical development and reproductive organ immaturity at doses greater than or equal to 2 mg/kg (approximately 1.2 to 5 times the clinical exposure by AUC at the recommended human dose). Decreased length of the femur and tibia persisted following 4 weeks of recovery. In general, the toxicologic profile of lenvatinib was similar between juvenile and adult rats, though toxicities including broken teeth at all dose levels and mortality at the 10 mg/kg/day dose level (attributed to primary duodenal lesions) occurred at earlier treatment time-points in juvenile rats.

8.5 Geriatric Use

Of 261 patients who received LENVIMA in Study 1, 118 (45.2%) were greater than or equal to 65 years of age and 29 (11.1%) were greater than or equal to 75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Of the 62 patients who received LENVIMA + everolimus in Study 2, 22 (35.5%) were greater than or equal to 65 years of age. Conclusions are limited due to the small sample size, but there appeared to be no overall differences in safety or effectiveness between these subjects and younger subjects.

8.6 Renal Impairment

No dose adjustment is recommended in patients with mild or moderate renal impairment. In patients with severe renal impairment, the recommended dose is 14 mg in the treatment of DTC and 10 mg in the treatment of RCC, either taken orally once daily. Patients with end stage renal disease were not studied.

8.7 Hepatic Impairment

No dose adjustment is recommended in patients with mild or moderate hepatic impairment. In patients with severe hepatic impairment, the recommended dose is 14 mg in the treatment of DTC and 10 mg in the treatment of RCC, either taken orally once daily.

10 OVERDOSAGE

There is no specific antidote for overdose with LENVIMA. Due to the high plasma protein binding, lenvatinib is not expected to be dialyzable. Adverse reactions in patients receiving single doses of LENVIMA as high as 40 mg were similar to the adverse events reported in the clinical studies at the recommended dose for DTC and RCC.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Hypertension:

Advise patients to undergo regular blood pressure monitoring and to contact their health care provider if blood pressure is elevated.

Cardiac Dysfunction:

Advise patients that LENVIMA can cause cardiac dysfunction and to immediately contact their healthcare provider if they experience any clinical symptoms of cardiac dysfunction such as shortness of breath or swelling of ankles.

Arterial Thrombotic Events:

Advise patients to seek immediate medical attention for new onset chest pain or acute neurologic symptoms consistent with myocardial infarction or stroke.

Hepatotoxicity:

Advise patients that they will need to undergo laboratory tests to monitor for liver function and to report any new symptoms indicating hepatic toxicity or failure.

Diarrhea

Advise patients when to start standard anti-diarrheal therapy and to maintain adequate hydration. Advise patients to contact their healthcare provider if they are unable to maintain adequate hydration.

Proteinuria and Renal Failure/Impairment:

Advise patients that they will need to undergo regular laboratory tests to monitor for kidney function and protein in the urine.

Gastrointestinal perforation or fistula formation:

Advise patients that LENVIMA can increase the risk of gastrointestinal perforation or fistula and to seek immediate medical attention for severe abdominal pain.

QTc Interval Prolongation

Advise patients who are at risk for QTc prolongation that they will need to undergo regular ECGs. Advise all patients that they will need to undergo laboratory tests to monitor electrolytes

Hemorrhagic Events:

Advise patients that LENVIMA can increase the risk for bleeding and to contact their healthcare provider for bleeding or symptoms of severe bleeding.

Embryofetal Toxicity:

Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy.

Advise females of reproductive potential to use effective contraception during treatment with LENVIMA and for at least 2 weeks following completion of therapy.

Lactation:

Advise nursing women to discontinue breastfeeding during treatment with LENVIMA.

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(continued from page 49)
months, they found an average growth rate of 0.13 cm per year.[2] 12% of the patients developed local progression (with the tumor size growing to a size of 4 cm or greater) and 1.1% developed metastatic disease.[2] One significant limitation of this study is that roughly 1/4th of the patients were removed from the study for various reasons, including patient or physician preference or loss to follow-up. This introduces a significant risk of selection bias. Additionally, the follow-up period, an average of 28 months, is relatively short, compared to many of the retrospective trials in the literature.

The other study by the RCCC (26), published approximately two months earlier, was a prospective trial of 82 patients with a renal mass 7 cm or smaller being followed under AS for a median of 36 months. Average initial mass size was 2.3 cm, and the largest mass at diagnosis was 5.4 cm.[26] 14.6% of the patients had DI after improvement of their comorbidities, patient decision after initial refusal to undergo surgery, or, in the case of 3 patients, because of rapid growth of their masses (mean rate of 1.07 cm per year).[26] All were found to have RCC on pathologic evaluation.[26] One patient developed metastatic disease after the tumor grew from 2.9 cm at diagnosis to 7.2 cm at a mean growth rate of 2.86 cm per year.[26] On average, the tumors in this trial grew at a rate of 0.25 cm per year.[26] No patients were removed from the trial or lost to follow-up but the trial was limited by relatively small sample size.

"Further prognostication of SRM using other biomarkers, namely those found in urine and serum, is in the early phases of research, but holds promise in providing non-invasive adjunctive information to imaging and PRB results. Aquaporin-1 and perilipin-2 are proteins that have been found in elevated quantities in the urine of patients with clear cell and papillary RCC, and have been shown to differentiate patients with those cancers from patients with chromophobe tumors, oncocytomas or angiomyolipomas."

The DISSRM Registry

DISSRM is a large prospective multi-institutional trial designed with multiple objectives: (a) to validate prior discoveries regarding AS and the natural history of SRM, (b) to objectively establish optimal eligibility criteria for AS, (c) to determine predictors of tumor aggressiveness, and (d) demonstrate the non-inferiority of AS to PI for SRM with regards to cancer-specific survival (CSS), overall survival (OS) and quality of life (QOL).[6,25]

All enrollees have a localized, solid, enhancing renal mass 4 cm or smaller in diameter, and no personal history of RCC or a known familial RCC syndrome.[25] Based on discussions with their urologist, patients may choose either PI or AS prior to enrollment.[25] PRB is an option for patients, if desired after a discussion with their urologist.[25] If undergoing AS, patients are imaged initially with cross sectional imaging and then reimaged, preferably with ultrasound (to decrease risk of radiation exposure from multiple CT scans,[6] approximately every 6 months for the first 2 years and every 1 year thereafter.[25] If an ultrasound incompletely images the mass or there is an unexpected change in the growth rate or changes in the qualitative appearance of the mass, trans-axial imaging is undertaken.[25] Patients on AS may switch to DI at any time but are recommended to undergo DI if they have progression. Progression in DISSRM is defined as a maximum diameter larger than 4.0 cm, a growth rate that exceeds 0.5 cm per year, or hematuria suspected to be from the SRM.[25]

The trial is ongoing, but at the time of the 2015 report[25] of its results, it was 5 years from its inception, with a median 2.1 years of follow-up for its 497 enrolled patients (the study currently enrolls over 600 patients). Of those patients, 55% chose PI and 45% chose AS. 9.4% of the AS cohort underwent DI.[25]

Compared to patients in the PI group, patients in the AS group were older, had more comorbidities, and had smaller tumors, in many situations with benign pathology on PRB.[25] Compared to patients in the AS group as a whole, patients going on to DI from AS had a lower proportion of patients with congestive heart failure and hypertension, and had larger tumors, a higher proportion of patients with multiple tumors, and a lower rate of PRB.[25]

The AS cohort experienced a median tumor growth rate of 0.11 cm per year, and approximately 16% of AS patients had progression, however none in that group developed metastatic disease during the trial.[25] Freedom from DI in the AS arm was 67% at 5 years, however DI was due to progression in only about 29% of the patients that group; the rest had DI because of patient preference.[25] Furthermore, of all the DI cases, only two tumors had a diagnosis of high grade RCC (25). Reassuringly, no patients in the DI arm experienced recurrence,[25] suggesting that properly-selected patients on AS may not 'lose their window of opportunity' to have complete extirpation if DI is triggered by signs of progression.

Five-year OS for PI was 92% vs. 75% for AS (including the DI group) (p=0.06); however, the CSS during this time period was 99% for PI and 100% for AS (p=0.3), reflecting the non-inferiority of AS to PI for oncologic control (in this limited follow-up period) and the relatively indolent nature of these renal masses, when compared to the competing comorbidities observed in these patients, especially in the AS cohort.[25]

Future Directions in Active Surveillance

Objective selection criteria In 2012, Jacobs et al.[27]showed that patients with more competing comorbidities, easier access to health care follow-up, smaller tumors, and tumors less amenable to partial nephrectomy are more likely to choose AS over PI. But what objective criteria should 'qualify' a patient for AS? Making this decision to undergo AS or PI involves weighing multiple factors each

with competing risks to the patient, and in many situations, the actual risks are not definitively known. These risks include the risk that the SRM is cancer, the risk that it will grow and/or metastasize, the chance of oncologic success and risk of complications from salvage chemotherapies if the cancer becomes metastatic, the oncologic risks of DI vs. PI, the risk of undergoing surgery (anesthetic risks, operative risks, post-operative risks), and the risks of competing comorbidities.

Ideally, we would be able to provide a patient with a sound recommendation for AS vs. PI based entirely on objective criteria. This would take a comprehensive understanding of the oncologic risks of AS, which in retrospective series appears to be equivalent to PI (in terms of CSS) in patients with high cardiovascular risk,[28] and which is currently being worked out in a prospective manner by DISSRM and others. With continued accumulation of prospective data on AS, the ideal patient for AS will become elucidated. This will take long-term outcomes data, to see how patients of a given risk category fair with one management strategy over another; this goal is a crucial aspect of DISSRM, and we look forward to reporting those results as the registry matures.

Quality of Life Published data in this realm are limited. In 2013, Parker et al.[29] at the University of Texas MD Anderson Cancer Center released the results of a prospective single-arm study of 100 patients on AS for T1-T2 renal masses. They reported that those with more illness uncertainty had worse QOL, as measured by validated questionnaires.[29] Preliminary data from DISSRM indicate that QOL in patients on AS, measured by the 12-Item Short Form Health Survey (SF-12), is worse than that of patients undergoing PI for the first two years of follow-up; after that, QOL is similar between the groups. Data from the 36-Item Short Form Health Survey (SF-36) on these patients show that the Physical Component Summary remains consistently worse for patients on AS than for patients undergoing PI for the first 4 years of follow up; however, the Mental Component Summary (which includes assessment of depression and anxiety) shows similar scores between the groups over the duration of the study. Of note, these preliminary data are not corrected for age or comorbidity, so there is risk for confounding. We hope that with further maturation of DISSRM, a greater understanding of QOL on AS can be ascertained.

Percutaneous Renal Mass Biopsy Currently, PRB is limited by subpar negative predictive values, intra-tumoral heterogeneity, and difficulty with differentiating cancer from benign tissue in certain situations, as described above. Molecular and genetic characterization of PRB tissue may be the new frontier in this area. This was described in a review of this topic by Volpe et al. in 2012.[30] Multiple immunohistochemical (IHC) and fluorescence in-situ hybridization (FISH) techniques have been developed, and used with varying success in PRB samples, to differentiate various subtypes of RCC, and to differentiate benign from malignant tissue, in many situations improving diagnostic accuracy over histologic examination alone.[30] These techniques hold promise in improving diagnostic and prognostic accuracy, but are still limited by intra-tumoral heterogeneity, which includes not just grade heterogeneity (as described above), but genetic heterogeneity as well, as described in a landmark study published by Gerlinger et al.[31] They showed that multiple sites within a single tumor had differing genetic profiles, linked by a branched evolutionary genetic pattern, with each profile suggesting different disease prognoses,[31] stark evidence of the limitations of random tumor sampling with PRB. Increasing numbers of PRB cores taken from a tumor may improve diagnostic yield, but is, of course, at the cost of increased risk for complications.

Molecular Studies Further prognostication of SRM using other biomarkers, namely those found in urine and serum, is in the early phases of research, but holds promise in providing non-invasive adjunctive information to imaging and PRB results. Aquaporin-1 and perilipin-2 are proteins that have been found in elevated quantities in the urine of patients with clear cell and papillary RCC, and have been shown to differentiate patients with those cancers from patients with chromophobe tumors, oncocytomas or angiomyolipomas.[32,33] Nuclear matrix protein-22 (NMP-22), kidney injury molecule-1 (KIM-1), and matrix metalloproteinases are other potential urinary targets of interest.[34] A large number of potential serum markers are being studied as well, including tumor necrosis factor receptor-associated factor-1, heat shock protein beta-1, serum amyloid A, gamma-glutamyl transferase, carbonic anhydrase IX, high sensitivity C-reactive protein, osteopontin, anti-hypoxia-inducible factor prolyl hydroxylase-3 antibody, pyruvate kinase type M2, and thymidine kinase 1.[34]

Imaging Another area of active research is in the use of imaging techniques to differentiate malignant from benign SRMs. One technique that holds considerable promise is technetium-99m–sestamibi single-photon emission computed tomography/x-ray computed tomography (^{99m}Tc-sestamibi SPECT/CT).[35] Gorin and colleagues showed that this imaging technique can differentiate clinical stage T1 renal oncocytomas and hybrid oncocytic/chromophobe tumors (HOCT) from multiple malignant tumor types.[35] This imaging technique may prove to be a powerful adjunct to the other techniques discussed above for preoperative diagnostic and prognostic determination for SRM.

Conclusions

SRM provide a considerable diagnostic and management dilemma, especially in those with limited cardiovascular reserve and life expectancy. PRB has growing diagnostic and prognostic role, and molecular characterization and advanced imaging techniques also hold promise in this realm. AS is in its infancy but preliminarily is showing

promising results as a safe way to manage these SRM in the appropriately selected patient. Ongoing prospective trials will hopefully further elucidate this issue.

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Case of Primary Renal Carcinoid Tumor in Healthy Military Soldier


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An otherwise healthy 25 year-old male presented to a civilian hospital emergency room with abdominal complaints. Contrasted Computed Tomography (CT) demonstrated an incidental large, solid enhancing right renal mass encompassing the upper pole and measuring 9.8 x8.4 x9.2cm with calcifications and cystic components. Imaging also demonstrated a 1.1cm paracaval node.

Further metastatic workup revealed a 1.1-cm right mediastinal/hilar lymph node and 3mm and 4mm right pulmonary nodules which were all found to be non-enhancing on PET/CT. MRI of his abdomen was also obtained due to concern on CT of possible invasion into the wall of the Inferior Vena Cava (IVC) which, on MRI, appeared to have a very small fat plane between the two structures.

Decision was made to perform a right robotic assisted laparoscopic radical nephrectomy with excision of pericaval lymph node(s) as an alternative to pure laparoscopy to aid in dissection of this mass from the IVC and dissection of the pericaval node. The patient recovered uneventfully except for a delayed post-operative non-Clostridrial right colitis. Pathology revealed a 10.5cm Carcinoid tumor with focal extension into the perinephric fat but no extension into the adrenal gland, pT3aN1Mx. Two pericaval nodes were both positive for metastatic carcinoid. The patient had no known other primary site.

The patient underwent urinary 5-HIAA evaluation which was negative and octreotide scintigraphy for evaluation of metastatic disease with focal radiotracer uptake within the left hepatic lobe. Diagnostic laparoscopy was undertaken by surgeons at a nearby regional tertiary care hospital with the possibility of left liver lobe resection but was found at that time to have multiple implants throughout the liver. These were biopsied and confirmed to be metastatic carcinoid. He currently is undergoing Sandostatin/octreotide therapy with oncology monthly. He continues to remain asymptomatic at 18 months post operatively.

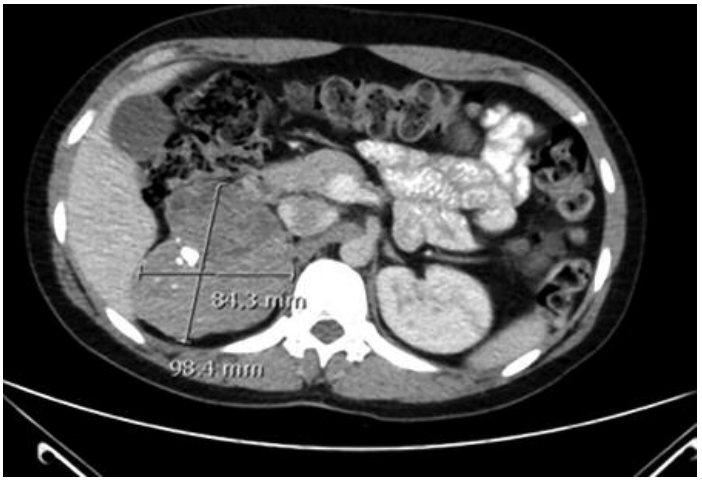

Figure 1. Right Renal Mass revealed on Contrasted Computed Tomography (CT).

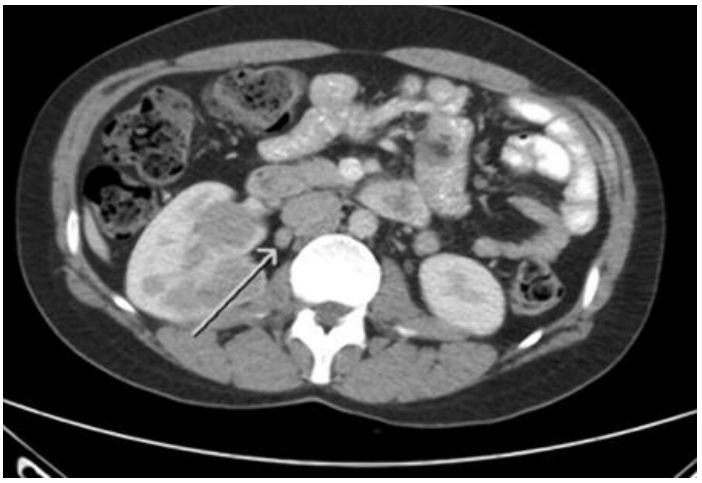
Figure 2. Paracaval Lymph Node.

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Carcinoid Tumor Found, A Rare Entity

Carcinoid is a rare neuroendocrine tumor typically found

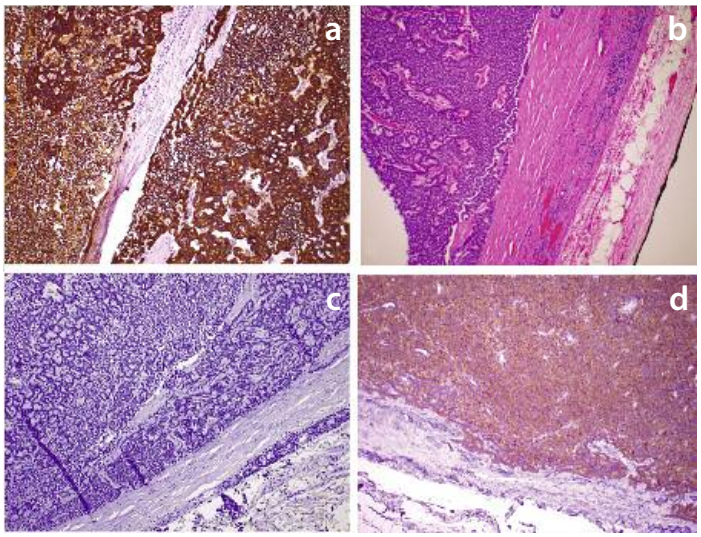

Figure 3. (a) Tumor cells are positive for immunostain CK 8/18 (magnification: ×200) (b) Microscopy revealing classical carcinoid organoid and tubulopapillary pattern with focal rosettes and delicate fibrovascular stroma (magnification: ×200). (c) Tumor cells are negative for immunostain chromogranin (magnification: ×200). (d) Tumor cells are positive for immunostain synaptophysin (magnification: ×200).

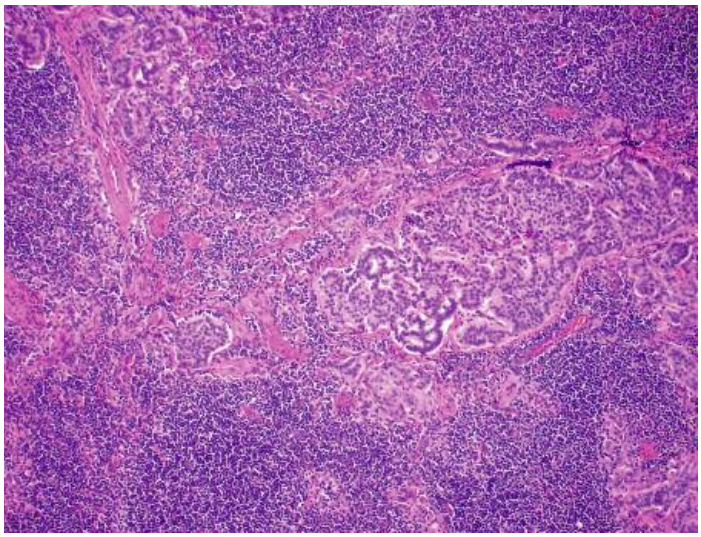

Figure 4. Lymph node involvement.

in the gastrointestinal tract, lungs, and the pancreas. Carcinoid tumors of the genitourinary tract are rare (<1%).[1] Although the most common genitourinary site is the testis or ovary, primary renal carcinoid has been described. Resnick et al first reported a carcinoid tumor of the kidney in 1966, and 81 cases since that time until 2012 have been reported in the English language literature.[2,3] A more recent search since 2012 reveals 8 cases worldwide (English and non-English). Typically, these tumors occur in adults (average age of 52) with no gender predominance.[4] Over 75% of these tumors are solitary and greater than 4cm (average size of 8.4 cm).[5,6,3] Patients most commonly present with flank pain, hematuria, and abdominal fullness/palpable mass.[7] Approx- imately 12% of patients will manifest carcinoid syndrome which includes symptoms of diarrhea, flushing, palpitations.[5,7]

Radical Nephrectomy Is Treatment of Choice

Radical nephrectomy with lymphadenectomy is the treatment of choice for carcinoid tumors of the kidney and can be curative for small tumors. However, at least 50% of patients will be found to have metastatic disease to lymph nodes, liver, and/or bone at the time of presentation.[7] Forty-five percent of patients will be found to have pT3 disease when metastatic disease is not present.[3] Even with metastatic disease, the behavior of the tumor can vary widely from patients succumbing to the disease within months to patients surviving for years.[3] Romero et al found that the mean disease free survival in their series was 43 months but patients with bone, liver, or contralateral kidney metastasis had a very poor prognosis.

Screening these patients for metastasis must be undertaken with somatostatin receptor (octreotide) scintigraphy since MRI and CT are not adequate to evaluate for low volume metastatic disease.[3] Octreotide is also the treatment of choice for patients with metastatic disease. A trial comparing octreotide vs placebo (PROMID trial) found an improved survival of 8.3 months with octreotide therapy, but this study examined only midgut carcinoid tumors.[3,8] Other chemotherapeutic drugs (cisplatin, 5-FU, etoposide) have proven unsuccessful.[3]

First Time Da Vinci System Used for Renal Carcinoid Tumor

This report stands as the first documented case utilizing the Da Vinci Robotic system for nephrectomy and lymphadenectomy for renal carcinoid tumor. Although a robotic approach can add setup time and expense to the case, we feel that robotic-assisted laparoscopy provides distinct advantages over pure laparoscopy in select cases of large tumors abutting the liver or great vessels such as in this case. The improved visualization, precision, and expanded instrumentation facilitates lymph node dissection and decreases risk of large vessel injury.

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Kidney Cancer Treatments March into the Future: A Renal Cell Review of ASCO 2016


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Prior to the advent of targeted therapies a decade ago, the treatment of metastatic kidney cancer was relatively stagnant. Since that time, explosions of knowledge and insight into the biological mechanisms that drive renal cell carcinoma have led to a steady stream of advancements. The last several months (RCC) have been no different with the approvals of carbozantinib, nivolumab, and levatinib (in combination with everolimus) being among the biggest headliners. The breakthroughs seen over these last few years have extended life for many patients and improved quality of life dramatically compared to the situation just a decade ago. Despite these remarkable advances, however, advanced RCC continues to be an incurable disease in the great majority of cases.

At the American Society of Clinical Oncology's 2016 annual meeting in Chicago, researchers and clinicians in the field look towards the future to further innovations and insights that will hopefully lead to even better outcomes for patients. A number of oral presentations, educational sessions, and posters highlighted recent findings.

Nivolumab Follow-Up—New Data Over 4 Years

Dr David McDermott discussed long-term overall survival (OS) with nivolumab in previously treated patients with advanced RCC from phase I and II studies. While nivolumab has been shown to prolong overall survival as compared to everolimus in the phase III CheckMate 025 study, the overall survival benefit in earlier studies was unclear. Dr McDermott presented follow-up data of greater than 4 years from these early studies, representing the longest follow-up in any PD–1/PD–L1 studies to date. Median OS in the phase I study was 22.4 months and median OS in the phase II study was 23.4 months. About one-third of patients treated with nivolumab were alive at 5 years in the phase I study and 3 years in the phase II study. The survival benefits noted were across all risks groups, including those who traditionally had poor outcomes.

Final Overall Survival from METEOR: Cabozantinib vs Everolimus

Toni Choueiri, MD, presented the final overall survival analysis from the METEOR trial, a randomized phase 3 trial of cabozantinib versus everolimus in patients with advanced RCC; 658 patients were randomized to receive either cabozantinib versus everolimus. The median OS was found to be 21.4 months in the carbozantinib group and 16.5 months for the everolimus group. Remarkably, this OS benefit was also consistently observed across all pre-specified subgroups, including across MSKCC risk stratification groups. An OS benefit was observed regardless of the number and type of prior VEGFR therapies, prior anti-PD-1/PD-L1 treatment, the location and extent of tumor metastases, and tumor MET expression levels.

Should Checkpoint Inhibition Be Continued Beyond Radiographic Progression?

One of the issues addressed during the meeting was the potential benefit of treatment of immunotherapy beyond radiographic progression. It is clear that traditional measurement of disease progression by RECIST criteria may not always capture patient benefit from PD-1 and PD-L1 inhibitors. Newer immunotherapy protocols often allow patients to continue treatment beyond radiographic progression as long as there is ongoing clinical benefit. However, the frequency of such clinical responses beyond radiographic progression is unknown, and whether this strategy is beneficial to patients remains unclear. Chana

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Weinstock, MD, and colleagues presented an analysis of subjects from the CheckMate 025 trial who received any treatment beyond radiographic progression. They found that 171 of patients treated with nivolumab in the study had treatment beyond radiographic progression.

The median treatment duration beyond radiographic progression was 3.2 months (range 0.1-23.4), and there were 5 patients (2.9% of those treated beyond progression) with a partial response after initially meeting RECIST-defined progression. The median survival in the 171 patients on the nivolumab arm treated beyond progression was 28.1 months, while the median survival was 25.0 months for the 134 patients did not continue it after progression. The group concluded that treatment beyond progression rarely benefited patients.

A similar analysis from the same trial was conducted by Bernard J. Escudier, MD, and colleagues, but came to fairly different conclusions. They found that the median duration of treatment with nivolumab after progression with the drug was 3.4 months and that of the 140 patients treated beyond progression who had imaging before and after progression, 14% had a greater than 30% tumor burden reduction after radiographic progression. The median overall survival was 28.1 months for those patients treated beyond progression versus only 15.0 months for those not treated beyond progression ($p=<0.001$). These authors concluded that treatment beyond progression with nivolumab can be associated with tumor shrinkage.

Walter Stadler, MD presented a very balanced presentation which analyzed both Weinstock's and Escudier's work. He detailed the differences in analyses undertaken by the two groups and concluded that while RECIST criteria should not define progression strictly, that those patients who seem to derive the greatest benefits from treatment beyond progression were those who had a "little bit" of progression as opposed to those who had overt progression with multiple new sites of disease, great enlargement of radiographic disease sites, or obvious clinical deterioration.

Cytoreductive Nephrectomy: Pros and Cons

The pros and cons of cytoreductive nephrectomy were debated in an educational session. Prior to the advent of targeted therapies, research supported cytoreductive nephrectomy in patients with metastatic renal cancer as compared with interferon therapy alone. But, clinical benefit of this strategy is not clear in the era of targeted therapy and in the emerging treatment landscape.

It is clear that a delay in systemic therapy in order to perform nephrectomy may negatively impact survival. [1] It is also clear, that patients with poor-risk disease or predicted survival less than 12 months are unlikely to benefit from nephrectomy. Interestingly, Surveillance, Epidemiology, and End Results Program database analysis revealed that 65% of patients with advanced renal cancer do not undergo nephrectomy as their initial treatment; however, the great majority of patients studied in clinical trials have had a nephrectomy. Therefore, much research is needed into outcomes in patients with metastatic RCC who do not undergo nephrectomy, as this population is woefully underrepresented in the current published literature.

Evolving Treatment Strategies with TKIs, Immuno-Oncology

A second educational session chaired by Tom Hutson, MD, focused on Systemic Treatment, Evolving TKIs, and Immuno-Oncology. In these sessions, the evolution of RCC treatments was reviewed. Particular attention was paid to combination therapies, a strategy which had failed to garner much benefit for patients in previous studies due to excessive toxicities, especially when VEGF-targeted TKIs were combined with mTOR inhibitors. The recent approval of the combination of a VEGF receptor inhibitor (lenvatinib) and an mTOR inhibitor (everolimus) is an exception. A phase II study of this combination randomized 153 patients with mRCC who had received one prior VEGF-targeted therapy to lenvatinib plus everolimus compared with lenvatinib monotherapy compared with everolimus monotherap.

Median PFS (per investigator assessment) was initially reported as 14.6 months for the combination arm, 7.4 months for the lenvatinib only arm, and 5.5 months for the everolimus arm. Both lenvatinib-containing arms were significantly longer in terms of PFS than the everolimus arm. Objective response rates also favored the combination arm (43% vs. 27% vs. 6%). These benefits were not without cost, as there was considerable toxicity in the combination arm necessitating that 71% of patients reduce their lenvatinib dose and 24% to discontinue due to toxicity.

Updated data using independent radiologic review showed a more modest benefit to the combination with PFS of 12.8 months and of 35% response rate.[2] Despite regulatory approval, the benefit of this combination is still unclear and will have to be investigated in larger trials.

Combinations of PD-1 Inhibitors

This educational session went on to explore early studies and emerging data with combinations using PD-1 inhibitors to treat metastatic RCC. The phase I/II CheckMate 016 study, for example, randomized patients to a combination of nivolumab along with sunitinib, pazopanib, or ipilimumab. The pazaopnib arm was not expanded due to unacceptable levels of hepatotoxicity, the sunitinib combination was not pursued due to very favorable results from the nivolumab plus ipilimumab arm. The combination of nivolumab plus ipilimumab was further explored in a expanded cohort which randomized randomized 94 patients to nivolumab 3 mg/kg + ipilumumab 1 mg/kg or nivolumab 1 mg/kg + ipilumumab 3 mg/kg for 4 doses, followed by maintenance nivolumab 3 mg/kg every 2 weeks until progression or toxicity.

Preliminary results were presented at ASCO 2015[2] and

although median OS was not reached in either arm, promising PFS results and response rates have led to a phase III trial examining nivolumab 3 mg/kg + ipilumumab 1 mg/kg in over 1,000 metastatic RCC patients. The trial has completed enrollment and results are eagerly awaited.

The reminder of this educational session focused on defining value in metatstatic renal cell carcinoma from minimizing toxicities to better defining endpoints in trials, especially with newer immunotherapies in which PFS does not necessarily provide a surrogate for survival.

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POSTERS

Highlighting a Broad Spectrum of Treatment Options

Nivolumab vs everolimus. Many of the abstracts presented as posters focused on increasing understanding and optimizing the use of newer targeted therapies and immunotherapy in advanced RCC.A poster by David Cella, et al examined quality of life and its relationship to OS in patients with advanced clear-cell RCC treated with nivolumab or everolimus in the phase III CheckMate 025 study. They found that patient treated with nivolumab experienced a significant difference in improvement in disease related symptoms as compared to those receiving everolimus (55% vs 37%). Furthermore they found that an improvement in quality of life or no change in quality of life was associated with prolonged survival in nivolumab treated patients.

Sunitinib vs pazopanib. An analysis of 7438 metastatic RCC patients from the international metastatic RCC database consortium (IMDC) compared outcomes in patients treated with either first line sunitinib (n=6519) or pazopanib (n=919) with an overall median follow-up of 40.4 months. The study found no difference in overall survival between those treated with sunitinib vs pazopanib (22.3 months vs 22.6 months respectively, p=0.65). There was also no PFS difference between sunitinib and pazopanib (8.4 months vs 8.3 months respectively, p=0.17). And, there was no difference in response rate between sunitinib and pazopanib either (30% vs 28% respectively, p=0.15). The group found no difference in any second-line treatment between the two groups or differences in PFS during second-line treatment. Importantly, the study did not focus on differences in tolerability or toxicity profiles, which were noted to be significant in the PISCES and COMPARZ trials.

Rechallenging with targeted therapy. Eric Voog and colleagues presented a poster regarding third and fourth line therapies in metastatic RCC. Of 270 patients receiving targeted therapies analyzed, they found that 106 and 58 were able to go on to receive third and fourth lines of therapy respectively. They also concluded that for patients who responded longer than six months to an earlier TKI, a rechallenge with the same targeted therapy in a subsequent line of therapy could provide high clinical benefit with acceptable toxicity.

Pazopanib and interferon-alpha as first line therapy. A Phase II study from the Spanish Oncology Genitourinary Group (SOGUG) tested a combination of pazopanib and interferon alpha in the first-line setting in 33 patients with advanced RCC. This study found a 27% partial response rate and 61% stable disease rate. Median PFS was 14.8 months (95% CI: 4.35-25.2) and median overall survival was not reached. The authors concluded that their results support further research of alternative combinations of pazopanib with new immunotherapeutic agents, which are more active and better tolerated than interferon alpha.

Alternating pazopanib and everolimus. A negative study worth noting is the ROPETAR trial, a phase II study which attempted to rotate patients with advanced RCC through bimonthly treatment cycles of an alternating tyronsine kinase inhibitor (pazopanib) with an mTOR inhibitor (everolimus) compared to standard pazopanib. It was theoretically suggested that such a strategy may lead to delayed drug resistance, however, the study found that rotating therapies did not lead to a delay in drug resistance, prolonged PFS, or less toxicity.

Novel agents in phase 2 development. A couple of posters reported results of studies with novel agents. For example, a group from China, tested anlotinib, an oral TKI which targets VEGFR1/2/3, FGFR2 in the first line setting for metastatic RCC. In this phase II trial researchers randomized 133 patients in a 2:1 fashion to anlotinib vs sunitinib. They found no major difference in efficacy with both groups having a similar median PFS (11.3 vs. 11.0 months and response rate (24.4% vs. 23.3%). Anlotinib appears to have a favorable safety profile in this population.

Funda Meric-Bernstam, Nizar Tannir, and colleagues presented a phase 1 study of CB-839, a small molecule inhibitor of glutaminase, tested alone and in combination with everolimus in patients with RCC. They reported that of 75 patients who received monotherapy with CB-839 at 600-1000 mg BID a low rate of grade 3 or 4 adverse events were noted (4/75 pts). Nineteen heavily pretreated (median of 3 prior therapies) RCC patients with various histologies (10 clear cell, 6 papillary, 3 other) were en-

rolled in this dosing cohort.

One of these RCC patients has achieved a confirmed partial response, which remains ongoing after 8.3 months on therapy. Radiographic response, including stable disease, was observed in 9 of 15 (60%) patients with imaging data available for evaluation. The authors concluded that CB-839 has been well tolerated and demonstrated evidence of efficacy in RCC patients, including an ongoing confirmed partial response, which has resulted in further expansion of this cohort. The combination of CB-839 with everolimus is still being studied.

Results in non-clear cell RCC. Other posters focused on outcomes in non-clear cell RCC and other variant histologies. Dr. Steven Yip and colleagues presented a poster reviewing outcomes of 114 metastatic chromophobe RCC treated in the targeted therapy era. Data was abstracted from the International Metastatic Renal Cell Cancer Database Consortium. These authors found that patients with metastatic chromophobe RCC had a similar outcomes, including overall survival, compared to patients with clear cell mRCC. Overall survival in the study group was 20.8 months (95% CI 19.9 - 21.7) vs 21.8 months (95% CI 20.9 - 22.9) for clear cell patients in this database. The overall response rate of targeted therapy in these chromophobe patients was 20% and 46% went on to receive second line systemic therapy.

Papillary RCC vs. clear cell. A similar study examined outcomes in papillary RCC using data from the International Metastatic Renal Cell Cancer Database Consortium. Of 5637 patients analyzed 466/5637 (8%) were found to have papillary histology. Overall survival was significantly lower in the papillary patients as compared to those with clear cell RCC (13.8 months vs 21.9 months). PFS was also lower for papillary patients (4.7 months vs 7.3 months). Sunitinib was the most common first line agent (62.9%), but no differences in survival were observed between various targeted therapies. Response rate to targeted therapy was 10.2% in papillary RCC patients compared to 30.5% in patients with clear cell disease. About half (49.5%) received second-line therapy.

Sunitinib results in sarcomatoid RCC. The results of the ECOG 1808 study, a randomized phase II trial of sunitinib with or without gemcitabine in advanced kidney cancer with sarcomatoid features were reported. The study randomized 47 patients to sunitinib in combination with gemcitabine , while 40 received standard of care sunitinib alone. Median progression free survival in the combination arm which 23.4 weeks (90% CI: 13.6–25.4 weeks) and 17 weeks (90% CI: 13.0 – 33.3 weeks) in the comparator arm. Median overall survival was 40.9 weeks (90% CI: 28.1–55.9 weeks) in the combination arm and 50.1 weeks (90% CI: 29.1–59.3 weeks) with sunitinib alone. Although the study failed to show a statistically significant difference between the two arms, there was a trend towards higher response rate (18.6% vs 10.8%) and longer duration of response in the combination arm.

Renal medullary carcinoma—20 years of data. Two posters focused on renal medullary carcinoma, a rare and highly aggressive kidney cancer that tends to impact younger patients with sickle cell trait. Maria Isabel Carlo and colleagues retrospectively reviewed the 36 cases who have presented over 20 years from Memorial Sloan Kettering Cancer Center. Median age was 28 years (range 12-72), most patients were male (75%), African American (70%; n = 20/29 with race reported) and presented with metastatic disease (83%). All had sickle cell trait.

Of the 23 patients with available tissue, all lacked SMARCB1 expression by IHC. Analysis with in-situ hybridization for SMARCB1 in 8 patients revealed loss of heterozygosity with concurrent translocation in 6, and biallelic loss in 2. Next-generation targeted sequencing (NGS) showed no VHL mutations. Overall survival in 32 evaluable patients was 5.8 months (95% CI 4.1-10.9). 11 patients received platinum-based therapy; 4 had a partial response, 2 had stable disease, 4 had progressive disease, 1 was non-evaluable. Their median PFS was 2.9 months. Three of the patients received VEGF or mTOR inhibitors, and none of these had a response. The authors concluded that loss of SMARCB1 is the key molecular feature in renal medullary carcinoma and suggested therefore that novel agents targeting chromatin remodeling, such as EZH2 inhibitors, should be explored in this disease.

Dr Jianjun Gao of MD Anderson Cancer Center led a group of researchers who performed whole-exome sequencing and single nucleotide polymorphism (SNP) analyses of 10 renal medullary carcinoma cases. They found frequent mutations in chromatin remodeling genes (7 of 10 cases), including mutations in the SMARCB1 and SMARCA5 genes. SNP analysis demonstrated that only the case with SMARCA5 somatic mutation harbored SMARCB1 monoallelic loss, but all of the cases had loss of SMARCB1 protein by immunohistochemistry. They further identified EZH2 as one of the top over-expressed upstream regulators. RT-PCR and western blot analyses confirmed that EZH2 expression is elevated at both mRNA and protein levels corresponding to SMARCB1 loss in RMC tumors.

An in vitro assessment of a novel RMC tumor cell line derived from the case harboring SMARCB1 deletion showed that the EZH2 inhibitor GSK343 inhibited proliferation of this cell line. The authors concluded that because only 30% of cases analyzed showed inactivation of SMARCB1 through somatic mutations or monoallelic loss, other additional epigenetic mechanisms may lead to gene inactivation in this disease. In addition, this data suggest that EZH2 may be a relevant therapeutic target in RMC.

DNA patterns and morphological phenotypes. A few posters focused on more basic science investigations. DNA methylation patterns were reported by Gabriel Mal-

ouf and colleagues. Because it was unknown if DNA methylation profiles correlated with morphological or ontological phenotypes, these researchers tested 22 diverse RCC specimens using deep profiling of DNA methylation via Digital Restriction Analysis of DNA Methylation (DREAM) technology based on next generation sequencing analysis of methylation-specific signatures.

They validated their findings in an independent dataset of diverse histopathological RCC subtypes (n = 44) and in The Cancer Genome Atlas Clear Cell (n = 424) and Chromophobe Renal Cell Carcinoma (n = 66) Datasets. They found two major epi-clusters: one which encompasses clear-cell RCC (n = 4), papillary RCC (n = 5), mucinous and spindle cell carcinomas (n = 2) and translocation RCC (n = 5); and the other which comprises oncocytoma (n = 2) and chromophobe RCC (n = 4). The authors concluded that these observations might be useful in the future to predict patient outcomes.

A German group investigated the contribution of interleukin-22 (IL22), a T cell secreted cytokine, to RCC progression and outcomes. They found that IL22 expression in RCC patients inversely correlates with median OS and PFS, and that higher IL-22 expression is associated with reduced median OS. The authors suggested that IL22 should be considered as a prognostic marker in RCC. They also note that their study provides evidence for potential negative effects of immunotherapy by inducing T cell-derived IL-22 in RCC.

Revisiting high-dose IL-2. Although attention in advanced RCC has recently been focused on newer targeted therapies and the potential promise of targeted immunotherapies, at least two posters examined a much older RCC therapy: high dose interleukin-2 (HD IL-2). One of the posters highlighted the 10 year experience of HD IL-2 outcomes from The Christie Hospital in Manchester, one of the world's leading centers for this therapy. The Christie authors presented data from 145 RCC patients treated with HD IL-2 in their center.

Among the cohort with favorable pathology (n = 106), an overall response rate of 48.1% was observed, with a complete response rate of 21.6% reported. The median OS was 49.4 months. Factors linked to significantly better response and/or survival included: > 50% alveolar growth pattern, higher cycle 1 tolerance (> 18 doses), < 3 metastatic organ sites , and > 6/12 duration between diagnosis and start of treatment. CAIX (Carbonic anhydrase 9) is prognostic but not predictive of response. Toxicities were manageable on general medical wards, and there were no treatment-related deaths. Most CRs were durable with 76% (23/30) remaining relapse-free (median 39 months follow up). The authors concluded that fit patients with favorable histology and low disease burden should be considered for HD IL 2, despite the availability of newer treatments.

HDAC inhibitor could enhance effect of IL-2. Roberto Pili and colleagues approached the HD IL-2 story from a different approach. They hypothesize that immunosuppressive factors such as regulatory T cells and myeloid-derived suppressive cells (MDSCs) limit the efficacy of immunotherapies, such as HD IL-2 and note that histone deacetylase (HDAC) inhibitors have been shown to have immunomodulatory effects. This group had previously reported that the HDAC inhibitor entinostat had synergistic effects in combination with HD IL-2 in a renal cell carcinoma model by down-regulating Foxp3 expression and function of regulatory T cells.

Pili and colleagues report the results of phase I/II study examining the combination of enitnostat and HD IL-2. Forty-seven patients have been enrolled and 38 completed one cycle of treatment. Of evaluable patients, 37%; achieved a response with 3 CRs noted. The overall median PFS for treatment-naïve clear cell patients was 13.8 months and the median PFS of responders was 28.5 months. The median OS to date was 65.3 months. The authors concluded that these suggest that entinostat may increase the therapeutic effect of high dose IL-2 by modulating immunosuppressive cells. KCJ

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of considerations underlying the use of these agents within the treatment algorithm for RCC. OBR provides similar information on other cancers as well as part of a broad spectrum of offerings.

What's on the horizon for virtual meetings and interactive initiatives? Consider the idea recently announced in June by the Association of Community Cancer Centers (ACCC). The ACCC unveiled a virtual community for Oncology Care Model (OCM) practices to share tips, tools, and resources as they navigate new transformational cancer care delivery and payment models. Through this one-of-a-kind online platform, invited practices will gain access to need-to-know information and leading experts on trending OCM issues. The community will foster robust dialogue and provide extensive peer-to-peer learning opportunities.

The online community is part of the ACCC OCM Collaborative, a broader effort to support OCM practices throughout implementation of the first oncology-specific payment reform model. The Collaborative provides a forum to share practical, how-to resources and best practices to assist in implementing and ultimately succeeding in the OCM. The Collaborative's new virtual community platform will enable OCM participants to share their experiences, challenges, and strategies in real time, learning from one another as they implement the model. As practices sign their participation agreements, look to the ACCC OCM Collaborative in the coming months for live meetings, conference calls, and more.

As exciting and provocative as all of these online initiatives and resources are, let's remember that we still need to attend scientific meetings in person, if possible. The exchange of ideas at the ASCO meeting and other gatherings remains the "real deal" and an invaluable experience and opportunity to exchange ideas. But virtual meetings are indeed, the next best thing to being there.

Robert A. Figlin, MD
Editor-in-Chief

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kinase inhibitors to receive 60 mg cabozantinib once a day or 10 mg everolimus once a day.
Conclusion: Treatment with cabozantinib increased overall survival, delayed disease progression, and improved the objective response compared with everolimus. Based on these results, cabozantinib should be considered as a new standard-of-care treatment option for previously treated patients with advanced RCC. Patients should be monitored for adverse events that might require dose modifications.

A Phase Ib Study of BEZ235, a Dual Inhibitor of Phosphatidylinositol 3-Kinase (PI3K) and Mammalian Target of Rapamycin (mTOR), in Patients With Advanced Renal Cell Carcinoma. Carlo MI, Molina AM, Lakhman Y, et al. *Oncologist.* 2016 Jun 10. pii: theoncologist.2016-0145.
Summary: Our results highlight additional toxicities of dual PI3K/mTOR inhibition in the clinical setting that were unforeseen from preclinical models. Because of toxicity and lack of efficacy, BEZ235 should not be further developed in the current formulation for patients with RCC. Allosteric inhibitors of the mammalian target of rapa-mycin complex 1 (mTORC1) are approved for advanced RCC. Preclinical models have suggested that dual inhibition of phosphatidylinositol 3-kinase (PI3K) and mTOR kinase may establish superior anticancer effect. The aim here was to establish safety for BEZ235, a potent inhibi-tor of both PI3K and mTOR, in advanced RCC. Patients with advanced RCC who had previously failed standard therapy received escalating doses of BEZ235 in sachet formulation twice daily until progression or unacceptable toxicity. Primary endpoints were to identify the maximally tolerated dose (MTD) and to determine the recommended dose for the phase 2 study. The study was terminated early because of high incidence of dose-limiting toxicities (DLTs) across all dose levels tested. Ten patients were treated with BEZ235-six with clear cell and four with non-clear cell subtypes. Two had stable disease as best response, and three had progressive disease.
Conclusion: BEZ235 twice daily resulted in significant toxicity without objective responses; further development of this compound will not be pursued in this disease.

Quality of Life in Patients With Advanced Renal Cell Carcinoma Given Nivolumab Versus Everolimus in CheckMate 025: a Randomised, Open-Label, Phase 3 Trial. Cella D, Grünwald V, Nathan P, et al. *Lancet Oncol.* 2016 Jun 3. pii: S1470-2045(16)30125-5. doi: 10.1016/S1470-2045(16)30125-5.
Summary: In the phase 3 CheckMate 025 study, previously treated patients with advanced RCC who were randomly assigned to nivolumab had an overall survival benefit compared with those assigned to everolimus. This trial compared health-related quality of life (HRQoL) between treatment groups. CheckMate 025 was an open-label study done at 146 oncology centers in 24 countries. Patients were randomly assigned to treatment between Oct 22, 2012, and March 11,2014. Patients with advanced RCC were randomly assigned (1:1, block size of four) to receive nivolumab every 2 weeks or everolimus once per day. The study was stopped early at the planned interim analysis in July, 2015, because the study met its primary endpoint. A protocol amendment permitted patients in the everolimus group to cross over to nivolumab treatment. All patients not on active study therapy are being followed up for survival. At the interim analysis, HRQoL was assessed with the Functional Assessment of Cancer Therapy-Kidney Symptom Index-Disease Related Symptoms (FKSI-DRS) and European Quality of Life (EuroQol)-5 Dimensions (EQ-5D) questionnaires. Pre-specified endpoints were to assess, in each treatment group, disease-related symptom progression rate based on the FKSI-DRS and changes in reported global health outcomes based on the EQ-5D. Analyses were powered according to the original study protocol, and the trial analyzed FKSI-DRS and EQ-5D data for all patients who underwent randomization and had a baseline assessment and at least one post-baseline assessment. HRQoL data were collected at baseline for 362 (88%) of 410 patients in the nivolumab group and 344 (84%) of 411 patients in the everolimus group. The mean difference in FKSI-DRS scores between the nivolumab and everolimus groups was 1·6 (95% CI 1·4-1·9; p<0·0001) with descriptive statistics and 1·7 (1·2-2·1; p<0·0001) with mixed-effects model repeated-measures analysis. In terms of FKSI-DRS score, more patients had a clinically meaningful (ie, an increase of at least 2 points from baseline) HRQoL improvement with nivolumab was significantly better (200 [55%] of 361patients) versus everolimus (126 [37%] of 343 patients; p<0·0001). Median time to HRQoL improvement was shorter in patients given nivolumab (4·7 months, 95% CI 3·7-7·5) than in patients given everolimus.
Conclusion: Nivolumab was associated with HRQoL improvement compared with everolimus in previously treated patients with advanced renal cell carcinoma. KCJ

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The TIVO-3 trial, together with the previously completed TIVO-1 trial of tivozanib in the first line treatment of RCC, is designed to support a first and third line indication for tivozanib in the US. Marketing authorization applications seeking approval of tivozanib as a treatment for first line renal cell cancer are currently pending in Europe and Russia based on applications submitted by AVEO's partners EUSA Pharma and Pharmstandard in those respective territories.

"While significant advances have been made in the treatment of renal cancer, there remains a need for effective yet more tolerable treatments, both for single agent and combination use," said Brian Rini, MD, Professor of Medicine at the Cleveland Clinic Lerner College of Medicine. "In past studies, tivozanib has demonstrated a unique tolerability profile among VEGF targeted therapies, owing to its high selectivity for the VEGF pathway, that have resulted in fewer dose interruptions or reductions. I am pleased to see tivozanib return to the clinic, with the goal of better understanding its single agent potential through TIVO-3, and I look forward to realizing its potential for combination use with checkpoint inhibitors in future studies."

ADAPT Trial Continues to Progress in Pivotal Phase 3 "Personalized Vaccine" Evaluation

DURHAM, NC—Argos Therapeutics Inc. has announced that the independent data monitoring committee (IDMC) for the company's pivotal Phase 3 ADAPT clinical trial of AGS-003 for the treatment of metastatic renal cell carcinoma (mRCC) has recommended the continuation of the trial based on results of the IDMC's scheduled interim data review. The next IDMC meeting is being planned to coincide with the Genitourinary Cancers Symposium in February 2017. ADAPT stands for for Autologous Dendritic Cell Immunotherapy (AGS-003) Plus Standard Treatment of Advanced Renal Cell Carcinoma (RCC).

"As the largest global Phase 3 trial ever performed in newly diagnosed, intermediate and poor risk mRCC patients, the ADAPT trial continues to progress," said Robert Figlin, MD, the Steven Spielberg Family chair in hematology oncology, professor of medicine and biomedical sciences at the Cedars-Sinai Samuel Oschin Comprehensive Cancer Institute and the co-principal investigator for the ADAPT trial. "With all the excitement regarding the clinical benefit of the emerging immuno-oncology therapies, a positive outcome of the ADAPT trial, because of AGS-003's novel mechanism of action, could be a game changer in the treatment of mRCC."

AGS-003 is an individualized immunotherapy that captures both mutated and variant antigens that are unique to each patient's tumor, and, therefore, specifically designed to induce an immune response targeting that patient's particular tumor antigens. In an open-label Phase 2 trial, treatment with AGS-003 plus sunitinib resulted in median overall survival of more than 30 months in newly diagnosed, intermediate and poor risk mRCC patients. We have enrolled a total of 462 mRCC patients in our ongoing pivotal, randomized Phase 3 ADAPT trial evaluating AGS-003 in combination with standard targeted therapy, which has a primary endpoint of overall survival.

Clinical Data on First-in-Class Oral HIF-2α Inhibitor in Patients with Advanced RCC Presented at 2016 ASCO Meeting

CHICAGO—The first-in-human Phase 1 clinical data on an investigational candidate, PT2385, were presented at the annual meeting of the American Society of Clinical Oncology (ASCO) . PT2385 is the first clinical stage antagonist of hypoxia inducible factor-2α (HIF-2α), a transcription factor implicated in the development and progression of kidney and other cancers. Peloton is the company evaluating the inhibitor.

In an oral presentation titled, "A Phase 1 Dose-Escalation Trial of PT2385, a first-in-class oral HIF-2α Inhibitor, in Patients with Advanced Clear Cell Renal Cell Carcinoma," it was shown that PT2385 was well tolerated with no dose-limiting toxicities and had pharmacologic activity with encouraging clinical efficacy. The key findings:

- PT2385 was well tolerated with no dose-limiting toxicities.
- Initial signs of efficacy include 1 complete responder, 3 partial responders, and stable disease in 16 patients for 16 or more weeks.
- To date, 10% of patients remain in the study for at least one year; the study is ongoing.

Patients with advanced clear cell renal cell carcinoma (ccRCC) and at least one prior therapy with a VEGF inhibitor were treated with PT2385 to determine the recommended Phase 2 dose and evaluate safety, pharmacokinetics and pharmacodynamics. Twenty-six patients were enrolled in dose escalation and received PT2385 from 100 to 1800 mg twice per day. Patients were heavily pretreated prior to study entry, with greater than 50 percent having four or more prior therapies. Exposure increased with doses up to the 800 mg cohort without a further increase from 800 to 1800 mg. No dose limiting toxicities were observed at any dose level. Circulating plasma levels of the HIF-2α transcriptional target erythropoietin (EPO) rapidly decreased with treatment with PT2385 and remained suppressed. Based on safety, pharmacokinetic and EPO pharmacodynamic data, 800 mg twice per day was selected as the recommended Phase 2 dose. An additional 25 patients were enrolled in an expansion cohort at the recommended Phase 2 dose.

Among the 51 patients in total, the most common all-grade adverse events (AEs) were anemia, peripheral edema and fatigue. No cardiovascular AEs were noted. To date, one patient had a complete response, three patients had a partial response, and 16 patients had stable disease for 16 or more weeks. KCJ

SUTENT® (sunitinib malate) IS INDICATED FOR THE TREATMENT OF ADVANCED RENAL CELL CARCINOMA (RCC).

capsules SUTENT® sunitinib malate

TAKE ON ADVANCED RCC

IMPORTANT SAFETY INFORMATION

- **Hepatotoxicity has been observed in clinical trials and post-marketing experience. This hepatotoxicity may be severe, and deaths have been reported.** Monitor liver function tests before initiation of treatment, during each cycle of treatment, and as clinically indicated. SUTENT should be interrupted for Grade 3 or 4 drug-related hepatic adverse events and discontinued if there is no resolution. Do not restart SUTENT if patients subsequently experience severe changes in liver function tests or have other signs and symptoms of liver failure
- **Women of childbearing potential** should be advised of the potential hazard to the fetus and to avoid becoming pregnant
- Given the potential for serious adverse reactions (ARs) in **nursing infants,** a decision should be made whether to discontinue nursing or SUTENT

Please see additional Important Safety Information and Brief Summary, including BOXED WARNING, on the following pages.

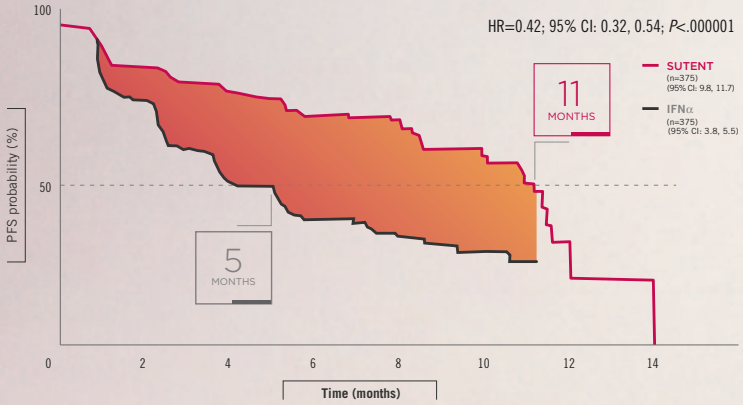
SUTENT® (sunitinib malate) IS INDICATED FOR THE TREATMENT OF ADVANCED RENAL CELL CARCINOMA (RCC).

DESIGNED FOR EFFICACY. ADJUSTABLE WHEN NEEDED.

SUTENT delivers proven efficacy. Dose adjustments may be made based on patient tolerability.

In the phase 3 trial, which allowed dose modifications, SUTENT demonstrated 11 months' median PFS in 1st-line mRCC

PRIMARY ENDPOINT



- **54%** of patients on SUTENT had **dose interruptions** and **52%** had **dose reductions** (vs 39% and 27% with IFNα, respectively)

Results are from the large (N=750), phase 3, randomized, multicenter trial comparing SUTENT with IFNα in patients with treatment-naïve mRCC. Primary endpoint was progression-free survival (PFS). Secondary endpoints included objective response rate (ORR), overall survival (OS), and safety.

- Patients were randomized to receive either 50-mg SUTENT once daily in cycles of 4 weeks on/2 weeks off (Schedule 4/2), or 9 MIU IFNα 3 times per week until disease progression or study withdrawal

IMPORTANT SAFETY INFORMATION (cont'd)

- **Cardiovascular events,** including heart failure, cardiomyopathy, myocardial ischemia, and myocardial infarction, some of which were fatal, have been reported. Use SUTENT with caution in patients who are at risk for, or who have a history of, these events. Monitor patients for signs and symptoms of congestive heart failure (CHF) and, in the presence of clinical manifestations, discontinuation is recommended. Patients who presented with cardiac events, pulmonary embolism, or cerebrovascular events within the previous 12 months were excluded from clinical studies
- SUTENT has been shown to **prolong QT interval** in a dose-dependent manner, which may lead to an increased risk for ventricular arrhythmias including **Torsades de Pointes,** which has been seen in <0.1% of patients. Monitoring with on-treatment electrocardiograms and electrolytes should be considered
- **Hypertension** may occur. Monitor blood pressure and treat as needed with standard antihypertensive therapy. In cases of severe hypertension, temporary suspension of SUTENT is recommended until hypertension is controlled
- There have been (<1%) reports, some fatal, of subjects presenting with seizures and radiological evidence of **reversible posterior leukoencephalopathy syndrome (RPLS)**
- **Hemorrhagic events,** including tumor-related hemorrhage such as pulmonary hemorrhage, have occurred. Some of these events were fatal. Perform serial complete blood counts (CBCs) and physical examinations
- Cases of **tumor lysis syndrome (TLS)** have been reported primarily in patients with high tumor burden. Monitor these patients closely and treat as clinically indicated
- **Thrombotic microangiopathy (TMA),** including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome, sometimes leading to renal failure or a fatal outcome, has been reported in patients who received SUTENT as monotherapy and in combination with bevacizumab. Discontinue SUTENT in patients developing TMA. Reversal of the effects of TMA has been observed after treatment was discontinued
- **Proteinuria** and nephrotic syndrome have been reported. Some of these cases have resulted in renal failure and fatal outcomes. Perform baseline and periodic urinalysis during treatment, with follow-up measurement of 24-hour urine protein as clinically indicated. Interrupt SUTENT and dose-reduce if 24-hour urine protein is ≥3 g; discontinue SUTENT in cases of nephrotic syndrome or repeat episodes of urine protein ≥3 g despite dose reductions

PP-SUT-USA-0200

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A well-known adverse reaction (AR) profile

In the phase 3, randomized, 1st-line mRCC trial vs IFNα (N=750)

THE MOST COMMON ARs occurring in ≥20% of patients receiving SUTENT for treatment-naïve metastatic RCC (all grades, vs IFNα)

Diarrhea (66% vs 21%), fatigue (62% vs 56%), nausea (58% vs 41%), anorexia (48% vs 42%), altered taste (47% vs 15%), mucositis/stomatitis (47% vs 5%), pain in extremity/limb discomfort (40% vs 30%), vomiting (39% vs 17%), bleeding, all sites (37% vs 10%), hypertension (34% vs 4%), dyspepsia (34% vs 4%), arthralgia (30% vs 19%), abdominal pain (30% vs 12%), rash (29% vs 11%), hand-foot syndrome (29% vs 1%), back pain (28% vs 14%), cough (27% vs 14%), asthenia (26% vs 22%), dyspnea (26% vs 20%), skin discoloration/yellow skin (25% vs 0%), peripheral edema (24% vs 5%), headache (23% vs 19%), constipation (23% vs 14%), dry skin (23% vs 7%), fever (22% vs 37%), and hair color changes (20% vs <1%)

THE MOST COMMON GRADE 3/4 ARs (occurring in ≥5% of patients with RCC receiving SUTENT vs IFNα)

Fatigue (15% vs 15%), hypertension (13% vs <1%), asthenia (11% vs 6%), diarrhea (10% vs <1%), hand-foot syndrome (8% vs 0%), dyspnea (6% vs 4%), nausea (6% vs 2%), back pain (5% vs 2%), pain in extremity/limb discomfort (5% vs 2%), vomiting (5% vs 1%), and abdominal pain (5% vs 1%)

THE MOST COMMON GRADE 3/4 LAB ABNORMALITIES (occurring in ≥5% of patients with RCC receiving SUTENT vs IFNα)

Lymphocytes (18% vs 26%), lipase (18% vs 8%), neutrophils (17% vs 9%), uric acid (14% vs 8%), platelets (9% vs 1%), hemoglobin (8% vs 5%), sodium decreased (8% vs 4%), leukocytes (8% vs 2%), glucose increased (6% vs 6%), phosphorus (6% vs 6%), and amylase (6% vs 3%)

Dosing overview

Recommended dose for advanced RCC is one 50-mg capsule taken orally once daily, on a schedule of 4 weeks on treatment followed by 2 weeks off

- Dose modification and/or dose interruption is recommended based on individual patient safety and tolerability
- SUTENT may be taken with or without food
- Remind patients to disclose any prescription or nonprescription medications they are taking, including bisphosphonates, vitamins, and herbal supplements, which can interact with SUTENT in different ways

When tolerability is a concern...

Dose modification per FDA label

For illustrative purposes only.

- The dose of SUTENT may be adjusted in 12.5-mg increments or decrements, based on individual patient safety and tolerability
- Dose adjustments are recommended when SUTENT is administered with CYP3A4 inhibitors or inducers. During treatment with SUTENT, patients should not drink grapefruit juice, eat grapefruit, or take St John's Wort
- No dose adjustment is recommended based on age, race, gender, body weight, creatinine clearance, ECOG performance status score, or hepatic impairment (Child-Pugh Class A or B)

Dose interruption considerations from retrospective studies

- In patients with advanced RCC who are unable to tolerate Schedule 4/2, consider the dose reduction described in the FDA-approved label or, as an alternative, consider modifying the schedule to 2 weeks on treatment followed by 1 week off (Schedule 2/1) using the same dose
  - —Studies supporting Schedule 2/1 have not been reviewed by the FDA. For most studies, the patient population was small and/or analysis was post hoc, and therefore susceptible to bias. The efficacy of any particular alternative dosing schedule has not been established[1-5]

IMPORTANT SAFETY INFORMATION (cont'd)

- **Severe cutaneous reactions** have been reported, including cases of erythema multiforme (EM), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), some of which were fatal. If signs or symptoms of EM, SJS, or TEN are present, SUTENT treatment should be discontinued. If a diagnosis of SJS or TEN is suspected, treatment must not be re-started. Necrotizing fasciitis, including fatal cases, has been reported, including of the perineum and secondary to fistula formation. Discontinue SUTENT in patients who develop necrotizing fasciitis
- **Thyroid dysfunction** may occur. Monitor thyroid function in patients with signs and/or symptoms of thyroid dysfunction, including hypothyroidism, hyperthyroidism, and thyroiditis, and treat per standard medical practice
- SUTENT has been associated with symptomatic **hypoglycemia,** which may result in loss of consciousness or require hospitalization. Reductions in blood glucose levels may be worse in patients with diabetes. Check blood glucose levels regularly during and after discontinuation of SUTENT. Assess whether antidiabetic drug dosage needs to be adjusted to minimize the risk of hypoglycemia
- **Osteonecrosis of the jaw (ONJ)** has been reported. Consider preventive dentistry prior to treatment with SUTENT. If possible, avoid invasive dental procedures, particularly in patients receiving bisphosphonates
- Cases of **impaired wound healing** have been reported. Temporary interruption of therapy with SUTENT is recommended in patients undergoing major surgical procedures
- **Adrenal hemorrhage** was observed in animal studies. Monitor adrenal function in case of stress such as surgery, trauma, or severe infection
- **CBCs** with platelet count and serum chemistries including phosphate should be performed at the beginning of each treatment cycle for patients receiving treatment with SUTENT
- Dose adjustments are recommended when SUTENT is administered with **CYP3A4 inhibitors or inducers.** During treatment with SUTENT, patients should not drink grapefruit juice, eat grapefruit, or take St John's Wort

Please see Brief Summary, including BOXED WARNING, on the following pages.

February 2016

Pfizer U.S. Pharmaceuticals

References: 1. Atkinson BJ, Kalra S, Wang X, et al. Clinical outcomes for patients with metastatic renal cell carcinoma treated with alternative sunitinib schedules. *J Urol.* 2014;191(3):611-618. **2.** Bjarnason GA, Khalil B, Hudson JM, et al. Outcomes in patients with metastatic renal cell cancer treated with individualized sunitinib therapy: correlation with dynamic microbubble ultrasound data and review of the literature. *Urol Oncol.* 2014;32(4):480-487. **3.** Kondo T, Takagi T, Kobayashi H, et al. Superior tolerability of altered dosing schedule of sunitinib with 2-weeks-on and 1-week-off in patients with metastatic renal cell carcinoma—comparison to standard dosing schedule of 4-weeks-on and 2-weeks-off. *Jpn J Clin Oncol.* 2014;44(3):270-277. **4.** Najjar YG, Mittal K, Elson P, et al. A 2 weeks on and 1 week off schedule of sunitinib is associated with decreased toxicity in metastatic renal cell carcinoma. *Eur J Cancer.* 2014;50(6):1084-1089. **5.** Bracarda S, Iacovelli R, Boni L, et al. Sunitinib administered on 2/1 schedule in patients with metastatic renal cell carcinoma: the RAINBOW analysis. *Ann Oncol.* 2015;26(10):2107-2113.

SUTENT® (SUNITINIB MALATE) CAPSULES, ORAL

Brief Summary of Prescribing Information

WARNING: HEPATOTOXICITY
Hepatotoxicity has been observed in clinical trials and post-marketing experience. This hepatotoxicity may be severe, and deaths have been reported. *[See Warnings and Precautions]*

INDICATION AND USAGE: SUTENT is indicated for the treatment of advanced renal cell carcinoma (RCC).

DOSAGE AND ADMINISTRATION

Recommended Dose. The recommended dose of SUTENT for advanced RCC is one 50 mg oral dose taken once daily, on a schedule of 4 weeks on treatment followed by 2 weeks off (Schedule 4/2). SUTENT may be taken with or without food.

Dose Modification. Dose interruption and/or dose modification in 12.5 mg increments or decrements is recommended based on individual safety and tolerability.

A dose reduction for SUTENT to a minimum of 37.5 mg daily should be considered if SUTENT must be co-administered with a strong CYP3A4 inhibitor.

A dose increase for SUTENT to a maximum of 87.5 mg daily should be considered if SUTENT must be co-administered with a CYP3A4 inducer. If dose is increased, the patient should be monitored carefully for toxicity.

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS

Hepatotoxicity. SUTENT has been associated with hepatotoxicity, which may result in liver failure or death. Liver failure has been observed in clinical trials (7/2281 [0.3%]) and post-marketing experience. Liver failure signs include jaundice, elevated transaminases and/or hyperbilirubinemia in conjunction with encephalopathy, coagulopathy, and/or renal failure. Monitor liver function tests (ALT, AST, bilirubin) before initiation of treatment, during each cycle of treatment, and as clinically indicated. SUTENT should be interrupted for Grade 3 or 4 drug-related hepatic adverse events and discontinued if there is no resolution. Do not restart SUTENT if patients subsequently experience severe changes in liver function tests or have other signs and symptoms of liver failure.

Safety in patients with ALT or AST >2.5 x ULN or, if due to liver metastases, >5.0 x ULN has not been established.

Pregnancy. SUTENT can cause fetal harm when administered to a pregnant woman. As angiogenesis is a critical component of embryonic and fetal development, inhibition of angiogenesis following administration of SUTENT should be expected to result in adverse effects on pregnancy. In animal reproductive studies in rats and rabbits, sunitinib was teratogenic, embryotoxic, and fetotoxic. There are no adequate and well-controlled studies of SUTENT in pregnant women. If the 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. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with SUTENT.

Cardiovascular Events. In the presence of clinical manifestations of congestive heart failure (CHF), discontinuation of SUTENT is recommended. The dose of SUTENT should be interrupted and/or reduced in patients without clinical evidence of CHF but with an ejection fraction <50% and >20% below baseline. Cardiovascular events, including heart failure, cardiomyopathy, myocardial ischemia, and myocardial infarction, some of which were fatal, have been reported. Use SUTENT with caution in patients who are at risk for, or who have a history of, these events. More patients treated with SUTENT experienced decline in left ventricular ejection fraction (LVEF) than patients receiving interferon-α (IFN-α).

In the treatment-naïve RCC study, 103/375 (27%) and 54/360 (15%) patients on SUTENT and IFN-α, respectively, had an LVEF value below the LLN. Twenty-six patients on SUTENT (7%) and seven on IFN-α (2%) experienced declines in LVEF to >20% below baseline and to below 50%. Left ventricular dysfunction was reported in four patients (1%) and CHF in two patients (<1%) who received SUTENT.

Patients who presented with cardiac events within 12 months prior to SUTENT administration, such as myocardial infarction (including severe/unstable angina), coronary/peripheral artery bypass graft, symptomatic CHF, cerebrovascular accident or transient ischemic attack, or pulmonary embolism were excluded from SUTENT clinical studies. It is unknown whether patients with these concomitant conditions may be at a higher risk of developing drug-related left ventricular dysfunction. Physicians are advised to weigh this risk against the potential benefits of the drug. **These patients should be carefully monitored for clinical signs and symptoms of CHF while receiving SUTENT. Baseline and periodic evaluations of LVEF should also be considered while these patients are receiving SUTENT. In patients without cardiac risk factors, a baseline evaluation of ejection fraction should be considered.**

QT Interval Prolongation and Torsade de Pointes. SUTENT has been shown to prolong the QT interval in a dose dependent manner, which may lead to an increased risk for ventricular arrhythmias including Torsade de Pointes. Torsade de Pointes has been observed in <0.1% of SUTENT-exposed patients.

SUTENT should be used with caution in patients with a history of QT interval prolongation, patients who are taking antiarrhythmics, or patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances. When using SUTENT, periodic monitoring with on-treatment electrocardiograms and electrolytes (magnesium, potassium) should be considered. Concomitant treatment with strong CYP3A4 inhibitors, which may increase sunitinib plasma concentrations, should be used with caution and dose reduction of SUTENT should be considered *[see Dosage and Administration]*.

Hypertension. Patients should be monitored for hypertension and treated as needed with standard anti-hypertensive therapy. In cases of severe hypertension, temporary suspension of SUTENT is recommended until hypertension is controlled.

Of patients receiving SUTENT for treatment-naïve RCC, 127/375 patients (34%) receiving SUTENT compared with 13/360 patients (4%) on IFN-α experienced hypertension. Grade 3 hypertension was observed in 50/375 treatment-naïve RCC patients (13%) on SUTENT compared to 1/360 patients (<1%) on IFN-α. No Grade 4 hypertension was reported. SUTENT dosing was reduced or temporarily delayed for hypertension in 21/375 patients (6%) on the treatment-naïve RCC study. Four treatment-naïve RCC patients, including one with malignant hypertension, discontinued treatment due to hypertension. Severe hypertension (>200 mmHg systolic or 110 mmHg diastolic) occurred in 32/375 treatment-naïve RCC patients (9%) on SUTENT and 3/360 patients (1%) on IFN-α.

Hemorrhagic Events. Hemorrhagic events reported through post-marketing experience, some of which were fatal, have included GI, respiratory, tumor, urinary tract and brain hemorrhages. In patients receiving SUTENT in a clinical trial for treatment-naïve RCC, 140/375 patients (37%) had bleeding events compared with 35/360 patients (10%) receiving IFN-α. Epistaxis was the most common hemorrhagic adverse event reported. Less common bleeding events included rectal, gingival, upper gastrointestinal, genital, and wound bleeding. Most events in RCC patients were Grade 1 or 2; there was one Grade 5 event of gastric bleed in a treatment-naïve patient.

Tumor-related hemorrhage has been observed in patients treated with SUTENT. These events may occur suddenly, and in the case of pulmonary tumors may present as severe and life-threatening hemoptysis or pulmonary hemorrhage. Cases of pulmonary hemorrhage, some with a fatal outcome, have been observed in clinical trials and have been reported in post-marketing experience in patients treated with SUTENT. Clinical assessment of these events should include serial complete blood counts (CBCs) and physical examinations.

Serious, sometimes fatal gastrointestinal complications including gastrointestinal perforation, have occurred rarely in patients with intra-abdominal malignancies treated with SUTENT.

Tumor Lysis Syndrome (TLS). Cases of TLS, some fatal, have occurred in patients treated with SUTENT. Patients generally at risk of TLS are those with high tumor burden prior to treatment. These patients should be monitored closely and treated as clinically indicated.

Thrombotic Microangiopathy. Thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome, sometimes leading to renal failure or a fatal outcome, has been reported in clinical trials and in post-marketing experience of SUTENT as monotherapy and in combination with bevacizumab. Discontinue SUTENT in patients developing TMA. Reversal of the effects of TMA has been observed after treatment was discontinued.

Proteinuria. Proteinuria and nephrotic syndrome have been reported. Some of these cases have resulted in renal failure and fatal outcomes. Monitor patients for the development or worsening of proteinuria. Perform baseline and periodic urinalyses during treatment, with follow up measurement of 24-hour urine protein as clinically indicated. Interrupt SUTENT and dose reduce for 24-hour urine protein ≥ 3 grams. Discontinue SUTENT for patients with nephrotic syndrome or repeat episodes of urine protein ≥ 3 grams despite dose reductions. The safety of continued SUTENT treatment in patients with moderate to severe proteinuria has not been systematically evaluated.

Dermatologic Toxicities. Severe cutaneous reactions have been reported, including cases of erythema multiforme (EM), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), some of which were fatal. If signs or symptoms of SJS, TEN, or EM (e.g., progressive skin rash often with blisters or mucosal lesions) are present, SUTENT treatment should be discontinued. If a diagnosis of SJS or TEN is suspected, SUTENT treatment must not be re-started.

Necrotizing fasciitis, including fatal cases, has been reported in patients treated with SUTENT, including of the perineum and secondary to fistula formation. Discontinue SUTENT in patients who develop necrotizing fasciitis.

Thyroid Dysfunction. Baseline laboratory measurement of thyroid function is recommended and patients with hypothyroidism or hyperthyroidism should be treated as per standard medical practice prior to the start of SUTENT treatment. All patients should be observed closely for signs and symptoms of thyroid dysfunction, including hypothyroidism, hyperthyroidism, and thyroiditis, on SUTENT treatment. Patients with signs and/or symptoms suggestive of thyroid dysfunction should have laboratory monitoring of thyroid function performed and be treated as per standard medical practice.

Hypothyroidism was reported as an adverse reaction in sixty-one patients (16%) on SUTENT in the treatment-naïve RCC study and in three patients (1%) in the IFN-α arm.

Cases of hyperthyroidism, some followed by hypothyroidism, have been reported in clinical trials and through post-marketing experience.

Hypoglycemia. SUTENT has been associated with symptomatic hypoglycemia, which may result in loss of consciousness, or require hospitalization. Hypoglycemia has occurred in clinical trials in 2% of the patients treated with SUTENT for RCC. Reductions in blood glucose levels may be worse in diabetic patients. Check blood glucose levels regularly during and after discontinuation of treatment with SUTENT. Assess if anti-diabetic drug dosage needs to be adjusted to minimize the risk of hypoglycemia.

Osteonecrosis of the Jaw (ONJ). ONJ has been observed in clinical trials and has been reported in post-marketing experience in patients treated with SUTENT. Concomitant exposure to other risk factors, such as bisphosphonates or dental disease, may increase the risk of osteonecrosis of the jaw.

Wound Healing. Cases of impaired wound healing have been reported during SUTENT therapy. Temporary interruption of SUTENT therapy is recommended for precautionary reasons in patients undergoing major surgical procedures. There is limited clinical experience regarding the timing of reinitiation of therapy following major surgical intervention. Therefore, the decision to resume SUTENT therapy following a major surgical intervention should be based upon clinical judgment of recovery from surgery.

Adrenal Function. Physicians prescribing SUTENT are advised to monitor for adrenal insufficiency in patients who experience stress such as surgery, trauma or severe infection.

Adrenal toxicity was noted in non-clinical repeat dose studies of 14 days to 9 months in rats and monkeys at plasma exposures as low as 0.7 times the AUC observed in clinical studies. Histological changes of the adrenal gland were characterized as hemorrhage, necrosis, congestion, hypertrophy and inflammation. In clinical studies, CT/MRI obtained in 336 patients after exposure to one or more cycles of SUTENT demonstrated no evidence of adrenal hemorrhage or necrosis. ACTH stimulation testing was performed in approximately 400 patients across multiple clinical trials of SUTENT. Among patients with normal baseline ACTH stimulation testing, one patient developed consistently abnormal test results during treatment that are unexplained and may be related to treatment with SUTENT. Eleven additional patients with normal baseline testing had abnormalities in the final test performed, with peak cortisol levels of 12-16.4 mcg/dL (normal >18 mcg/dL) following stimulation. None of these patients were reported to have clinical evidence of adrenal insufficiency.

Laboratory Tests. CBCs with platelet count and serum chemistries including phosphate should be performed at the beginning of each treatment cycle for patients receiving treatment with SUTENT.

ADVERSE REACTIONS

The data described below reflect exposure to SUTENT in 660 patients who participated in the double-blind treatment phase of a placebo-controlled trial (n=202) for the treatment of gastrointestinal stromal tumor (GIST), an active-controlled trial (n=375) for the treatment of RCC or a placebo-controlled trial (n=83) for the treatment of pancreatic neuroendocrine tumors (pNET). The RCC patients received a starting oral dose of 50 mg daily on Schedule 4/2 in repeated cycles.

The most common adverse reactions (≥20%) in patients with GIST, RCC or pNET are fatigue, asthenia, fever, diarrhea, nausea, mucositis/stomatitis, vomiting, dyspepsia, abdominal pain, constipation, hypertension, peripheral edema, rash, hand-foot syndrome, skin discoloration, dry skin, hair color changes, altered taste, headache, back pain, arthralgia, extremity pain, cough, dyspnea, anorexia, and bleeding. The potentially serious adverse reactions of hepatotoxicity, left ventricular dysfunction, QT interval prolongation, hemorrhage, hypertension, thyroid dysfunction, and adrenal function are discussed in *Warnings and Precautions*. Other adverse reactions occurring in RCC studies are described below.

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.

Adverse Reactions in the Treatment-Naïve RCC Study. The as-treated patient population for the treatment-naïve RCC study included 735 patients, 375 randomized to SUTENT and 360 randomized to IFN-α. The median duration of treatment was 11.1 months (range: 0.4 - 46.1) for SUTENT treatment and 4.1 months (range: 0.1 - 45.6) for IFN-α treatment. Dose interruptions occurred in 202 patients (54%) on SUTENT and 141 patients (39%) on IFN-α. Dose reductions occurred in 194 patients (52%) on SUTENT and 98 patients (27%) on IFN-α. Discontinuation rates due to adverse reactions were 20% for SUTENT and 24% for IFN-α. Most treatment-emergent adverse reactions in both study arms were Grade 1 or 2 in severity. Grade 3 or 4 treatment-emergent adverse reactions were reported in 77% versus 55% of patients on SUTENT versus IFN-α, respectively.

The following table compares the incidence of common (≥10%) treatment-emergent adverse reactions for patients receiving SUTENT versus IFN-α.

Adverse Reactions Reported in at Least 10% of Patients with RCC Who Received SUTENT or IFN-α*

	SUTENT (n=375)		IFN-α (n=360)	
Adverse Reaction, n (%)	**All Grades**	**Grade 3/4[a]**	**All Grades**	**Grade 3/4[b]**
Any	372 (99)	290 (77)	355 (99)	197 (55)
Constitutional				
Fatigue	233 (62)	55 (15)	202 (56)	54 (15)
Asthenia	96 (26)	42 (11)	81 (22)	21 (6)
Fever	84 (22)	3 (1)	134 (37)	1 (<1)
Weight decreased	60 (16)	1 (<1)	60 (17)	3 (1)
Chills	53 (14)	3 (1)	111 (31)	0 (0)
Chest Pain	50 (13)	7 (2)	24 (7)	3 (1)
Influenza like illness	18 (5)	0 (0)	54 (15)	1 (<1)
Gastrointestinal				
Diarrhea	246 (66)	37 (10)	76 (21)	1 (<1)
Nausea	216 (58)	21 (6)	147 (41)	6 (2)
Mucositis/stomatitis	178 (47)	13 (3)	19 (5)	2 (<1)
Vomiting	148 (39)	19 (5)	62 (17)	4 (1)
Dyspepsia	128 (34)	8 (2)	16 (4)	0 (0)
Abdominal pain[c]	113 (30)	20 (5)	42 (12)	5 (1)
Constipation	85 (23)	4 (1)	49 (14)	1 (<1)
Dry mouth	50 (13)	0 (0)	27 (7)	1 (<1)
GERD/reflux esophagitis	47 (12)	1 (<1)	3 (1)	0 (0)
Flatulence	52 (14)	0 (0)	8 (2)	0 (0)
Oral pain	54 (14)	2 (<1)	2 (1)	0 (0)
Glossodynia	40 (11)	0 (0)	2 (1)	0 (0)
Hemorrhoids	38 (10)	0 (0)	6 (2)	0 (0)
Cardiac				
Hypertension	127 (34)	50 (13)	13 (4)	1 (<1)
Edema, peripheral	91 (24)	7 (2)	17 (5)	2 (1)
Ejection fraction decreased	61 (16)	10 (3)	19 (5)	6 (2)

Adverse Reactions Reported in at Least 10% of Patients with RCC Who Received SUTENT or IFN-α* (cont'd)

Adverse Reaction, n (%)	SUTENT (n=375)		IFN-α (n=360)	
	All Grades	Grade 3/4[a]	All Grades	Grade 3/4[b]
Dermatology				
Rash	109 (29)	6 (2)	39 (11)	1 (<1)
Hand-foot syndrome	108 (29)	32 (8)	3 (1)	0 (0)
Skin discoloration/ yellow skin	94 (25)	1 (<1)	0 (0)	0 (0)
Dry skin	85 (23)	1 (<1)	26 (7)	0 (0)
Hair color changes	75 (20)	0 (0)	1 (<1)	0 (0)
Pruritus	44 (12)	1 (<1)	24 (7)	1 (<1)
Neurology				
Altered taste[d]	178 (47)	1 (<1)	54 (15)	0 (0)
Headache	86 (23)	4 (1)	69 (19)	0 (0)
Dizziness	43 (11)	2 (<1)	50 (14)	2 (1)
Musculoskeletal				
Back pain	105 (28)	19 (5)	52 (14)	7 (2)
Arthralgia	111 (30)	10 (3)	69 (19)	4 (1)
Pain in extremity/ limb discomfort	150 (40)	19 (5)	107 (30)	7 (2)
Endocrine				
Hypothyroidism	61 (16)	6 (2)	3 (1)	0 (0)
Respiratory				
Cough	100 (27)	3 (1)	51 (14)	1 (<1)
Dyspnea	99 (26)	24 (6)	71 (20)	15 (4)
Nasopharyngitis	54 (14)	0 (0)	8 (2)	0 (0)
Oropharyngeal Pain	51 (14)	2 (<1)	9 (2)	0 (0)
Upper respiratory tract infection	43 (11)	2 (<1)	9 (2)	0 (0)
Metabolism/Nutrition				
Anorexia[e]	182 (48)	11 (3)	153 (42)	7 (2)
Hemorrhage/Bleeding				
Bleeding, all sites	140 (37)	16 (4)[f]	35 (10)	3 (1)
Psychiatric				
Insomnia	57 (15)	3 (<1)	37 (10)	0 (0)
Depression[g]	40 (11)	0 (0)	51 (14)	5 (1)

*Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0
[a]Grade 4 ARs in patients on SUTENT included back pain (1%), arthralgia (<1%), dyspnea (<1%), asthenia (<1%), fatigue (<1%), limb pain (<1%) and rash (<1%).
[b]Grade 4 ARs in patients on IFN-α included dyspnea (1%), fatigue (1%), abdominal pain (<1%) and depression (<1%).
[c]Includes flank pain
[d]Includes ageusia, hypogeusia and dysgeusia
[e]Includes decreased appetite
[f]Includes one patient with Grade 5 gastric hemorrhage
[g]Includes depressed mood

Treatment-emergent Grade 3/4 laboratory abnormalities are presented below.

Laboratory Abnormalities Reported in at Least 10% of Treatment-Naïve RCC Patients Who Received SUTENT or IFN-α

Laboratory Parameter, n (%)	SUTENT (n=375)		IFN-α (n=360)	
	All Grades*	Grade 3/4*[a]	All Grades*	Grade 3/4*[b]
Gastrointestinal				
AST	211 (56)	6 (2)	136 (38)	8 (2)
ALT	192 (51)	10 (3)	144 (40)	9 (2)
Lipase	211 (56)	69 (18)	165 (46)	29 (8)
Alkaline phosphatase	171 (46)	7 (2)	132 (37)	6 (2)
Amylase	130 (35)	22 (6)	114 (32)	12 (3)
Total bilirubin	75 (20)	3 (1)	8 (2)	0 (0)
Indirect bilirubin	49 (13)	4 (1)	3 (1)	0 (0)
Renal/Metabolic				
Creatinine	262 (70)	2 (<1)	183 (51)	1 (<1)
Creatine kinase	183 (49)	9 (2)	40 (11)	4 (1)
Uric acid	173 (46)	54 (14)	119 (33)	29 (8)
Calcium decreased	156 (42)	4 (1)	145 (40)	4 (1)
Phosphorus	116 (31)	22 (6)	87 (24)	23 (6)
Albumin	106 (28)	4 (1)	72 (20)	0 (0)
Glucose increased	86 (23)	21 (6)	55 (15)	22 (6)
Sodium decreased	75 (20)	31 (8)	55 (15)	13 (4)
Glucose decreased	65 (17)	0 (0)	43 (12)	1 (<1)
Potassium increased	61 (16)	13 (3)	61 (17)	15 (4)
Calcium increased	50 (13)	2 (<1)	35 (10)	5 (1)
Potassium decreased	49 (13)	3 (1)	7 (2)	1 (<1)
Sodium increased	48 (13)	0 (0)	38 (10)	0 (0)
Hematology				
Neutrophils	289 (77)	65 (17)	178 (49)	31 (9)
Hemoglobin	298 (79)	29 (8)	250 (69)	18 (5)
Platelets	255 (68)	35 (9)	85 (24)	2 (1)
Lymphocytes	256 (68)	66 (18)	245 (68)	93 (26)
Leukocytes	293 (78)	29 (8)	202 (56)	8 (2)

*Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0
[a]Grade 4 laboratory abnormalities in patients on SUTENT included uric acid (14%), lipase (3%), neutrophils (2%), lymphocytes (2%), hemoglobin (2%), platelets (1%), amylase (1%), ALT (<1%), creatine kinase (<1%), creatinine (<1%), glucose increased (<1%), calcium decreased (<1%), phosphorous (<1%), potassium increased (<1%), and sodium decreased (<1%).
[b]Grade 4 laboratory abnormalities in patients on IFN-α included uric acid (8%), lymphocytes (2%), lipase (1%), neutrophils (1%), amylase (<1%), calcium increased (<1%), glucose decreased (<1%), potassium increased (<1%) and hemoglobin (<1%).

Venous Thromboembolic Events. Thirteen (3%) patients receiving SUTENT for treatment-naïve RCC had venous thromboembolic events reported. Seven (2%) of these patients had pulmonary embolism, one was Grade 2 and six were Grade 4, and six (2%) patients had DVT, including three Grade 3. One patient was permanently withdrawn from SUTENT due to pulmonary embolism; dose interruption occurred in two patients with pulmonary embolism and one with DVT. In treatment-naïve RCC patients receiving IFN-α, six (2%) venous thromboembolic events occurred; one patient (<1%) experienced a Grade 3 DVT and five patients (1%) had pulmonary embolism, all Grade 4.

Reversible Posterior Leukoencephalopathy Syndrome. There have been reports (<1%), some fatal, of subjects presenting with seizures and radiological evidence of reversible posterior leukoencephalopathy syndrome (RPLS). None of these subjects had a fatal outcome to the event. Patients with seizures and signs/symptoms consistent with RPLS, such as hypertension, headache, decreased alertness, altered mental functioning, and visual loss, including cortical blindness should be controlled with medical management including control of hypertension. Temporary suspension of SUTENT is recommended; following resolution, treatment may be resumed at the discretion of the treating physician.

Pancreatic and Hepatic Function. If symptoms of pancreatitis or hepatic failure are present, patients should have SUTENT discontinued. Pancreatitis was observed in 5 (1%) patients receiving SUTENT for treatment-naïve RCC compared to 1 (<1%) patient receiving IFN-α. Hepatotoxicity was observed in patients receiving SUTENT *[See Boxed Warning and Warnings and Precautions].*

Post-marketing Experience. The following adverse reactions have been identified during post-approval use of SUTENT. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and lymphatic system disorders: hemorrhage associated with thrombocytopenia*. Suspension of SUTENT is recommended; following resolution, treatment may be resumed at the discretion of the treating physician.

Gastrointestinal disorders: esophagitis.

Hepatobiliary disorders: cholecystitis, particularly acalculous cholecystitis.

Immune system disorders: hypersensitivity reactions, including angioedema.

Infections and infestations: serious infection (with or without neutropenia)*; necrotizing fasciitis, including of the perineum*. The infections most commonly observed with sunitinib treatment include respiratory, urinary tract, skin infections and sepsis/septic shock.

Musculoskeletal and connective tissue disorders: fistula formation, sometimes associated with tumor necrosis and/or regression*; myopathy and/or rhabdomyolysis with or without acute renal failure*. Patients with signs or symptoms of muscle toxicity should be managed as per standard medical practice.

Renal and urinary disorders: renal impairment and/or failure*; proteinuria; rare cases of nephrotic syndrome. Baseline urinalysis is recommended, and patients should be monitored for the development or worsening of proteinuria. The safety of continued SUTENT treatment in patients with moderate to severe proteinuria has not been systematically evaluated. Discontinue SUTENT in patients with nephrotic syndrome.

Respiratory disorders: pulmonary embolism*.

Skin and subcutaneous tissue disorders: pyoderma gangrenosum, including positive dechallenges; erythema multiforme and Stevens-Johnson syndrome.

Vascular disorders: arterial thromboembolic events*. The most frequent events included cerebrovascular accident, transient ischemic attack and cerebral infarction.

*including some fatalities

DRUG INTERACTIONS

CYP3A4 Inhibitors. Strong CYP3A4 inhibitors such as ketoconazole may **increase** sunitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme inhibition potential is recommended. Concurrent administration of SUTENT with the strong CYP3A4 inhibitor, ketoconazole, resulted in 49% and 51% increases in the combined (sunitinib + primary active metabolite) C_{max} and $AUC_{0-\infty}$ values, respectively, after a single dose of SUTENT in healthy volunteers. Co-administration of SUTENT with strong inhibitors of the CYP3A4 family (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) may increase sunitinib concentrations. Grapefruit may also increase plasma concentrations of sunitinib. A dose reduction for SUTENT should be considered when it must be co-administered with strong CYP3A4 inhibitors *[see Dosage and Administration].*

CYP3A4 Inducers. CYP3A4 inducers such as rifampin may **decrease** sunitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme induction potential is recommended. Concurrent administration of SUTENT with the strong CYP3A4 inducer, rifampin, resulted in a 23% and 46% reduction in the combined (sunitinib + primary active metabolite) C_{max} and $AUC_{0-\infty}$ values, respectively, after a single dose of SUTENT in healthy volunteers. Co-administration of SUTENT with inducers of the CYP3A4 family (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, St. John's Wort) may decrease sunitinib concentrations. St. John's Wort may decrease sunitinib plasma concentrations unpredictably. Patients receiving SUTENT should not take St. John's Wort concomitantly. A dose increase for SUTENT should be considered when it must be co-administered with CYP3A4 inducers *[see Dosage and Administration].*

In Vitro Studies of CYP Inhibition and Induction. *In vitro* studies indicated that sunitinib does not induce or inhibit major CYP enzymes. The *in vitro* studies in human liver microsomes and hepatocytes of the activity of CYP isoforms CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, and CYP4A9/11 indicated that sunitinib and its primary active metabolite are unlikely to have any clinically relevant drug-drug interactions with drugs that may be metabolized by these enzymes.

USE IN SPECIFIC POPULATIONS

Pregnancy. Pregnancy Category D *[see Warnings and Precautions].*
Sunitinib was evaluated in pregnant rats (0.3, 1.5, 3.0, 5.0 mg/kg/day) and rabbits (0.5, 1, 5, 20 mg/kg/day) for effects on the embryo. Significant increases in the incidence of embryolethality and structural abnormalities were observed in rats at the dose of 5 mg/kg/day (approximately 5.5 times the systemic exposure [combined AUC of sunitinib + primary active metabolite] in patients administered the recommended daily doses [RDD]). Significantly increased embryolethality was observed in rabbits at 5 mg/kg/day while developmental effects were observed at ≥1 mg/kg/day (approximately 0.3 times the AUC in patients administered the RDD of 50 mg/day). Developmental effects consisted of fetal skeletal malformations of the ribs and vertebrae in rats. In rabbits, cleft lip was observed at 1 mg/kg/day and cleft lip and cleft palate were observed at 5 mg/kg/day (approximately 2.7 times the AUC in patients administered the RDD). Neither fetal loss nor malformations were observed in rats dosed at ≤3 mg/kg/day (approximately 2.3 times the AUC in patients administered the RDD).

Sunitinib (0.3, 1.0, 3.0 mg/kg/day) was evaluated in a pre- and postnatal development study in pregnant rats. Maternal body weight gains were reduced during gestation and lactation at doses ≥1 mg/kg/day but no maternal reproductive toxicity was observed at doses up to 3 mg/kg/day (approximately 2.3 times the AUC in patients administered the RDD). At the high dose of 3 mg/kg/day, reduced body weights were observed at birth and persisted for offspring of both sexes during the pre-weaning period and in males during post-weaning period. No other developmental toxicity was observed at doses up to 3 mg/kg/day (approximately 2.3 times the AUC in patients administered the RDD).

Nursing Mothers. Sunitinib and its metabolites are excreted in rat milk. In lactating female rats administered 15 mg/kg, sunitinib and its metabolites were extensively excreted in milk at concentrations up to 12-fold higher than in plasma. It is not known whether this drug or its primary active metabolite are 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 SUTENT, 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 SUTENT in pediatric patients have not been established.

Physeal dysplasia was observed in cynomolgus monkeys with open growth plates treated for ≥ 3 months (3 month dosing 2, 6, 12 mg/kg/day; 8 cycles of dosing 0.3, 1.5, 6.0 mg/kg/day) with sunitinib at doses that were >0.4 times the RDD based on systemic exposure (AUC). In developing rats treated continuously for 3 months (1.5, 5.0 and 15.0 mg/kg) or 5 cycles (0.3, 1.5, and 6.0 mg/kg/day), bone abnormalities consisted of thickening of the epiphyseal cartilage of the femur and an increase of fracture of the tibia at doses ≥ 5 mg/kg (approximately 10 times the RDD based on AUC). Additionally, caries of the teeth were observed in rats at >5 mg/kg. The incidence and severity of physeal dysplasia were dose-related and were reversible upon cessation of treatment; however, findings in the teeth were not. A no effect level was not observed in monkeys treated continuously for 3 months, but was 1.5 mg/kg/day when treated intermittently for 8 cycles. In rats the no effect level in bones was ≤ 2 mg/kg/day.

Geriatric Use. Of 825 GIST and RCC patients who received SUTENT on clinical studies, 277 (34%) were 65 and over. No overall differences in safety or effectiveness were observed between younger and older patients.

Hepatic Impairment. No dose adjustment to the starting dose is required when administering SUTENT to patients with Child-Pugh Class A or B hepatic impairment. Sunitinib and its primary metabolite are primarily metabolized by the liver. Systemic exposures after a single dose of SUTENT were similar in subjects with mild or moderate (Child-Pugh Class A and B) hepatic impairment compared to subjects with normal hepatic function. SUTENT was not studied in subjects with severe (Child-Pugh Class C) hepatic impairment. Studies in cancer patients have excluded patients with ALT or AST >2.5 x ULN or, if due to liver metastases, >5.0 x ULN.

Renal Impairment. No adjustment to the starting dose is required when administering SUTENT to patients with mild, moderate, and severe renal impairment. Subsequent dose modifications should be based on safety and tolerability *[see Dose Modification].* In patients with end-stage renal disease (ESRD) on hemodialysis, no adjustment to the starting dose is required. However, compared to subjects with normal renal function, the sunitinib exposure is 47% lower in subjects with ESRD on hemodialysis. Therefore, the subsequent doses may be increased gradually up to 2 fold based on safety and tolerability.

OVERDOSAGE

Treatment of overdose with SUTENT should consist of general supportive measures. There is no specific antidote for overdosage with SUTENT. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage. Cases of accidental overdose have been reported; these cases were associated with adverse reactions consistent with the known safety profile of SUTENT, or without adverse reactions. A case of intentional overdose involving the ingestion of 1,500 mg of SUTENT in an attempted suicide was reported without adverse reaction. In non-clinical studies mortality was observed following as few as 5 daily doses of 500 mg/kg (3000 mg/m^2) in rats. At this dose, signs of toxicity included impaired muscle coordination, head shakes, hypoactivity, ocular discharge, piloerection and gastrointestinal distress. Mortality and similar signs of toxicity were observed at lower doses when administered for longer durations.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility. The carcinogenic potential of sunitinib has been evaluated in two species: rasH2 transgenic mice and Sprague-Dawley rats. There were similar positive findings in both species. In rasH2 transgenic mice gastroduodenal carcinomas and/or gastric mucosal hyperplasia, as well as an increased incidence of background hemangiosarcomas were observed at doses of ≥25 mg/kg/day following daily dose administration of sunitinib in studies of 1- or 6-months duration. No proliferative changes were observed in rasH2 transgenic mice at 8 mg/kg/day. Similarly, in a 2-year rat carcinogenicity study, administration of sunitinib in 28-day cycles followed by 7-day dose-free periods resulted in findings of duodenal carcinoma at doses as low as 1 mg/kg/day (approximately 0.9 times the AUC in patients given the RDD of 50 mg/day). At the high dose of 3 mg/kg/day (approximately 7.8 times the AUC in patients at the RDD of 50 mg/day) the incidence of duodenal tumors was increased and was accompanied by findings of gastric mucous cell hyperplasia and by an increased incidence of pheochromocytoma and hyperplasia of the adrenal medulla. Sunitinib did not cause genetic damage when tested in *in vitro* assays (bacterial mutation [AMES Assay], human lymphocyte chromosome aberration) and an *in vivo* rat bone marrow micronucleus test.

Effects on the female reproductive system were identified in a 3-month repeat dose monkey study (2, 6, 12 mg/kg/day), where ovarian changes (decreased follicular development) were noted at 12 mg/kg/day (≥ 5.1 times the AUC in patients administered the RDD), while uterine changes (endometrial atrophy) were noted at ≥2 mg/kg/day (≥ 0.4 times the AUC in patients administered the RDD). With the addition of vaginal atrophy, the uterine and ovarian effects were reproduced at 6 mg/kg/day in the 9-month monkey study (0.3, 1.5 and 6 mg/kg/day administered daily for 28 days followed by a 14 day respite; the 6 mg/kg dose produced a mean AUC that was ≥ 0.8 times the AUC in patients administered the RDD). A no effect level was not identified in the 3 month study; 1.5 mg/kg/day represents a no effect level in monkeys administered sunitinib for 9 months.

Although fertility was not affected in rats, SUTENT may impair fertility in humans. In female rats, no fertility effects were observed at doses of ≤5.0 mg/kg/day [(0.5, 1.5, 5.0 mg/kg/day) administered for 21 days up to gestational day 7; the 5.0 mg/kg dose produced an AUC that was ≥ 5 times the AUC in patients administered the RDD], however significant embryolethality was observed at the 5.0 mg/kg dose. No reproductive effects were observed in male rats dosed (1, 3 or 10 mg/kg/day) for 58 days prior to mating with untreated females. Fertility, copulation, conception indices, and sperm evaluation (morphology, concentration, and motility) were unaffected by sunitinib at doses ≤10 mg/kg/day (the 10 mg/kg/day dose produced a mean AUC that was ≥ 25.8 times the AUC in patients administered the RDD).

PATIENT COUNSELING INFORMATION

Gastrointestinal Disorders. Gastrointestinal disorders such as diarrhea, nausea, stomatitis, dyspepsia, and vomiting were the most commonly reported gastrointestinal events occurring inpatients who received SUTENT. Supportive care for gastrointestinal adverse events requiring treatment may include anti-emetic or anti-diarrheal medication.

Skin Effects. Skin discoloration possibly due to the drug color (yellow) occurred in approximately one third of patients. Patients should be advised that depigmentation of the hair or skin may occur during treatment with SUTENT. Other possible dermatologic effects may include dryness, thickness or cracking of skin, blister or rash on the palms of the hands and soles of the feet. Severe dermatologic toxicities including Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis have been reported. Patients should be advised to immediately inform their healthcare provider if severe dermatologic reactions occur.

Other Common Events. Other commonly reported adverse events included fatigue, high blood pressure, bleeding, swelling, mouth pain/irritation and taste disturbance.

Osteonecrosis of the Jaw. Prior to treatment with SUTENT, a dental examination and appropriate preventive dentistry should be considered. In patients being treated with SUTENT, who have previously received or are receiving bisphosphonates, invasive dental procedures should be avoided, if possible.

Hypoglycemia. Patients should be advised of the signs, symptoms, and risks associated with hypoglycemia that may occur during treatment with SUTENT. Hypoglycemia may be more severe in patients with diabetes taking antidiabetic medications. Severe hypoglycemia including loss of consciousness or requiring hospitalization has been reported. Patients should be advised to immediately inform their healthcare provider if severe signs or symptoms of hypoglycemia occur.

Thrombotic Microangiopathy. Thrombotic microangiopathy leading to renal insufficiency and neurologic abnormalities was observed in patients who received SUTENT as monotherapy or in combination with bevacizumab. Patients should be advised that signs and symptoms of thrombotic microangiopathy may occur during treatment with SUTENT. Patients should be advised to immediately inform their healthcare provider if signs and symptoms of thrombotic microangiopathy occur.

Proteinuria. Proteinuria and nephrotic syndrome has been reported. Patients should be advised that urinalysis will be performed prior to starting as well as during treatment with SUTENT. In cases with impact to renal function, treatment with SUTENT may be interrupted or discontinued.

Concomitant Medications. Patients should be advised to inform their health care providers of all concomitant medications, including over-the-counter medications and dietary supplements *[see Drug Interactions]*.

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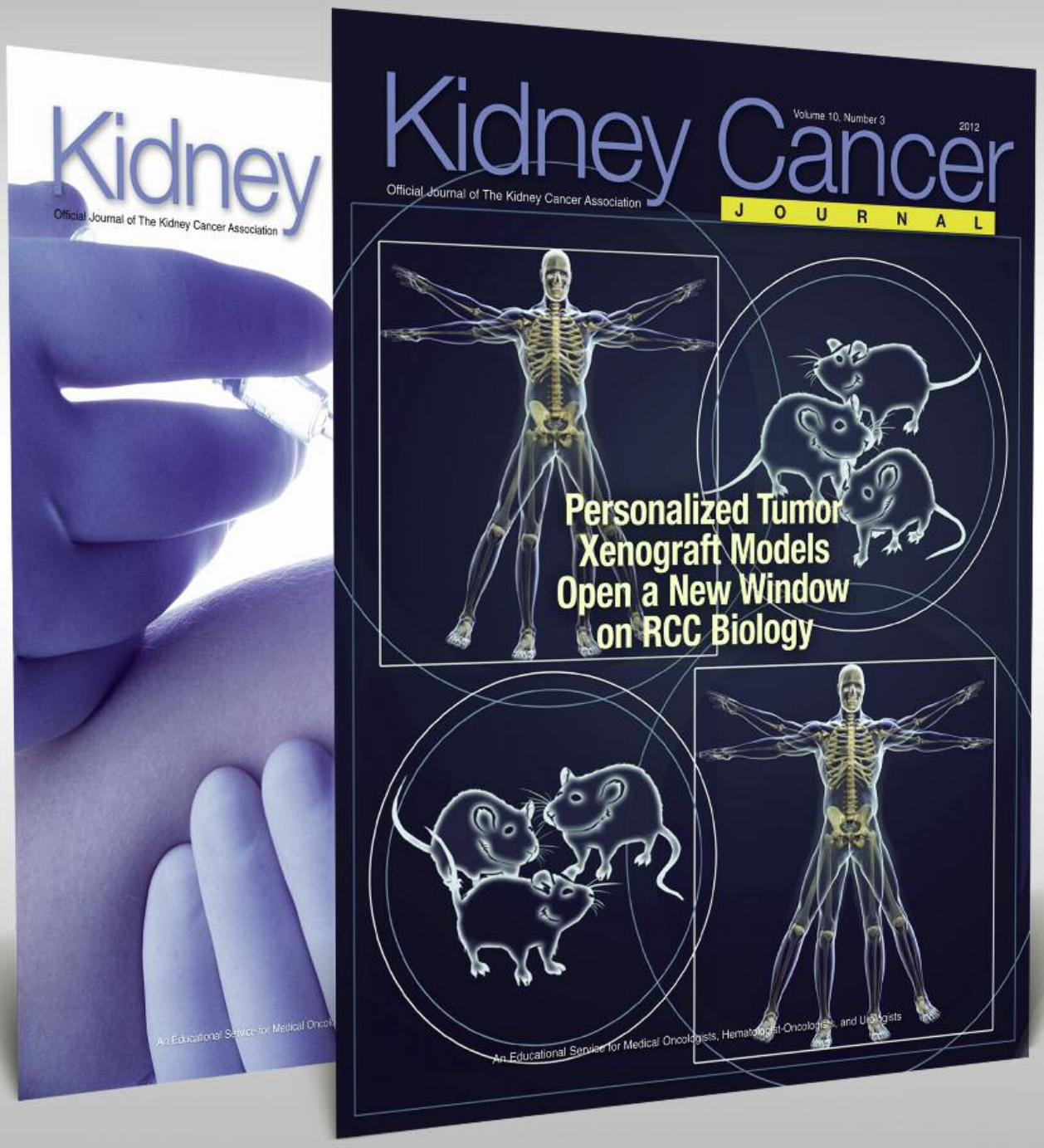

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