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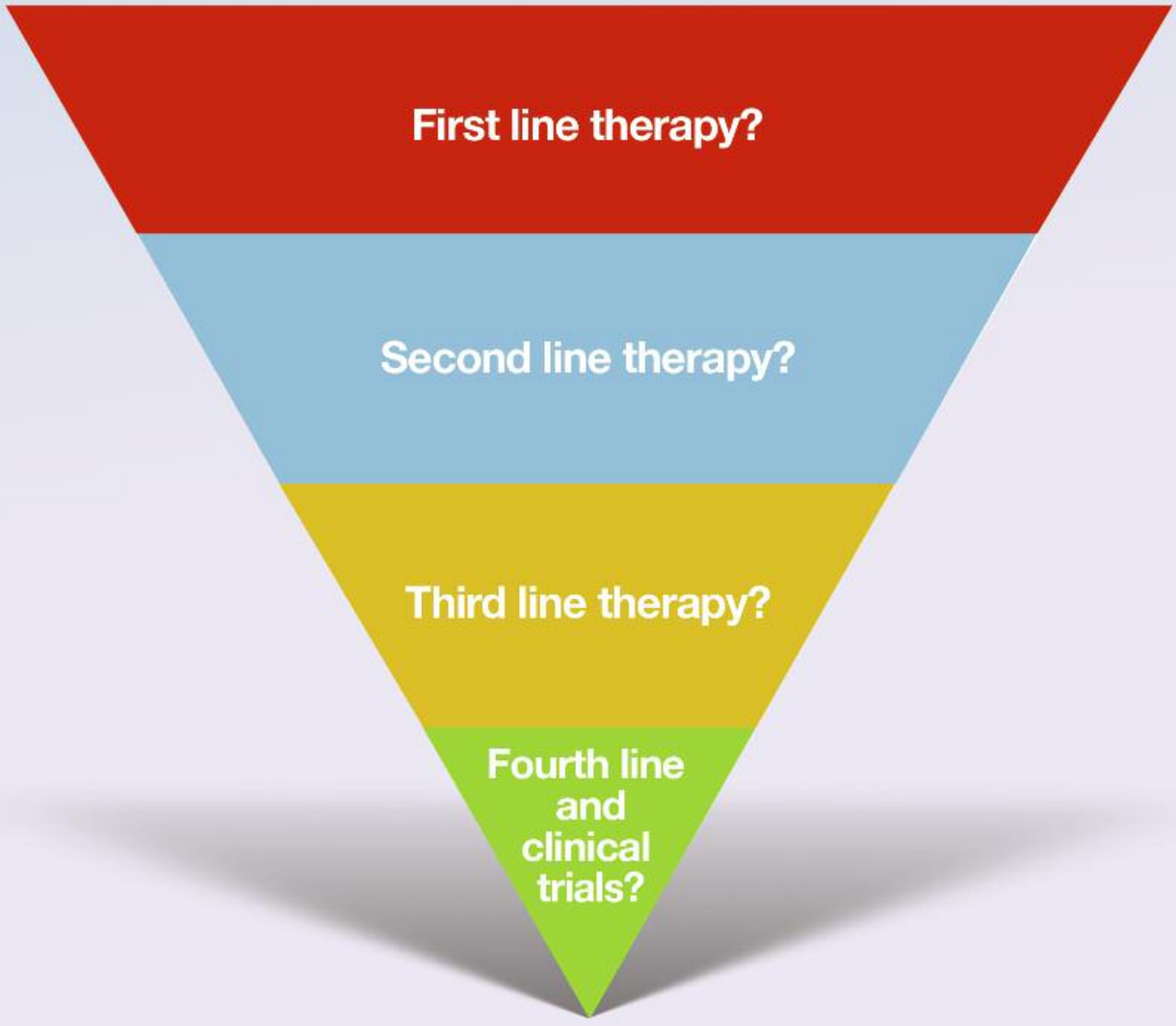
Rebuilding the Treatment Paradigm With New Pivotal Trial Data

Statins and Targeted Therapy: Is There a Consensus on Survival Outcomes?

Case Report: Long-Term Response With Autologous, Dendritic Cell-Based Immunotherapy



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

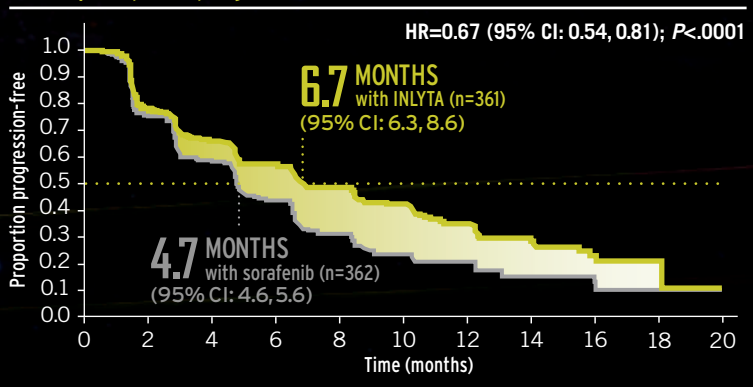
GIVE THEM A FIGHTING SECOND CHANCE

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 impact of pivotal trials on the paradigm of treatment is suggested by this image. Strategies for frontline therapy and beyond will be reshaped by emerging data as new drugs are approved and combinations of therapy explored.

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KCJ GUEST EDITOR'S MEMO

Shooting at a Rapidly Moving Target


Edwin M. Posadas, MD, FACP

"Exciting development." Practice-changing." Unprecedented." These are the bold terms frequently used to characterize recent developments in the treatment of renal cell carcinoma (RCC). In the past five years, we have come a long way. Ten years ago, we had a limited repertoire of cytokines which were difficult to use and beneficial to a very limited subset of patients. Now we have more than 11 effective treatments with 8 therapies that were approved in the past five years.

Most impressively, in the past six months, we have approved three new therapies. That has been the change, according to Thomas E. Hutson, DO, PharmD, Director of the Genitourinary Oncology Program, Charles A. Sammons Cancer Center at Baylor University Medical Center, Houston, whose comments were recently posted in an online interview.

Until recent times, effective agents were approved for their impact on progression free survival (PFS). Both cabozantinib and lenvatinib (in concert wither everolimus) have demonstrated improvement not only in PFS but also overall survival (OS) in studies with an active control arm. Nivolumab, a potent checkpoint inhibitor, was also shown to be active in kidney cancer. Interesting, this agent was found to improve OS with a more modest effect on PFS. This is a significant evaluation and advance for the field. Even with this progress, more new data continues to emerge.

Since much of this was reported out in the last six months, it will take us time to sort through this accumulated data and to determine how we can optimally utilize these agents in our patients. However, it is clear that all three of these therapies have an important role to play in patient management. As the field moves forward, so does the discussion on the integration of these approaches into the existing paradigm.

If you are fortunate to attend all or any of the major international oncology meetings this year and early in 2017, the treatment paradigm for renal cell carcinoma will be comprehensively discussed, analyzed, and debated. The first of these is already upon us: the European Society of Oncology (ESMO) meeting in Copenhagen, Denmark. Additional results from CABOSUN will be reviewed at this conference. Toni Choueiri, MD, the Principal Investigator on this trial has noted, "The positive outcome of CABOSUN is extremely exciting, as it marks the very first time that a therapy has shown a progression-free survival benefit over standard of care first-line treatment sunitinib for patients with previously untreated advanced renal cell carcinoma." Results from this trial will be

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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.

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Contact information

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

Peer Review and Editing

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

Conflict of Interest

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

Manuscript Preparation

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

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

References

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

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Essential Peer-Reviewed Reading in Kidney Cancer

The peer-reviewed articles summarized in this section were selected by the Guest Editor, Edwin M. Posadas, MD, for their timeliness, importance, relevance, and potential impact on clinical practice or translational research.

Small-molecule targeting of E3 ligase adaptor SPOP in kidney cancer. Guo, ZQ, Zheng T, Chen B, et al. *Cancer Cell*. 2016 Sep12; 30(3):474-84.
Summary: In the cytoplasm of virtually all clear-cell renal cell carcinoma (ccRCC), speckle-type POZ protein (SPOP) is overexpressed and misallocated, which may induce proliferation and promote kidney tumorigenesis. In normal cells, however, SPOP is located in the nucleus and induces apoptosis. Here we show that a structure-based design and subsequent hit optimization yield small molecules that can inhibit the SPOP-substrate protein interaction and can suppress oncogenic SPOP-signaling pathways. These inhibitors kill human ccRCC cells that are dependent on oncogenic cytoplasmic SPOP. Notably, these inhibitors minimally affect the viability of other cells in which SPOP is not accumulated in the cytoplasm.
Conclusion: The findings validate the SPOP-substrate protein interaction as an attractive target specific to ccRCC that may yield novel drug discovery efforts.

Targeting renal cell carcinoma with a HIF-2 antagonist. Chen W, Hill H, Christie A, et al. *Nature*. 2016 Sep 5.
Summary: Clear cell Renal Cell Carcinoma (ccRCC) is characterized by VHL inactivation[1,2]. Because no other gene is mutated as frequently, and VHL mutations are truncal[3], VHL inactivation is regarded as the governing event[4]. VHL loss activates HIF-2, and constitutive HIF-2 restores tumorigenesis in VHL-reconstituted ccRCC cells[5]. HIF-2 is implicated in angiogenesis and multiple other processes[6,7,8,9], but angiogenesis is the main target of drugs like sunitinib[10]. HIF-2, a transcription factor, has been regarded as undruggable[11]. A structure-based design approach identified a selective HIF-2 antagonist (PT2399) that we evaluate using a tumorgraft (TG)/PDX platform[12,13]. PT2399 dissociated HIF-2 (an obligatory heterodimer [HIF-2 /HIF-1])[14] in human ccRCC suppressing tumorigenesis in 56% (10/18) lines. PT2399 had greater activity than sunitinib, was active in sunitinib-progressing tumors, and was better tolerated. Unexpectedly, some VHL-mutant ccRCCs were resistant. Resistance occurred despite HIF-2 dissociation in tumors and evidence of Hif-2 inhibition in the mouse as determined by suppression of circulating erythropoietin, a HIF-2 target[15] and possible pharmacodynamic marker. We identified a HIF-2-dependent gene signature in sensitive tumors. Illustrating drug specificity, gene expression was largely unaffected by PT2399 in resistant tumors. Sensitive tumors exhibited a distinguishing gene expression signature, and generally higher HIF-2 levels. Prolonged PT2399 treatment led to resistance. We identified a binding site and second site suppressor mutation in HIF-2 and HIF-1 respectively. Both mutations preserved HIF-2 dimers despite PT2399. Finally, an extensively pretreated patient with a sensitive TG had disease control for >11 months with the close analogue PT2385.
Conclusion: This study validates HIF-2 as a target in ccRCC, shows that some ccRCC are, unexpectedly, HIF-2 independent, and sets the stage for biomarker-driven clinical trials.

Partial nephrectomy versus radical nephrectomy for clinical T1b and T2 renal tumors: a systematic review and meta-analysis of comparative studies. Mir MC, Derweesh I, Porpiglia F, et al. *Eur Urol*. 2016 Sep 7.
Summary: Partial nephrectomy (PN) is the reference standard of management for a cT1a renal mass. However, its role in the management of larger tumors (cT1b and cT2) is still under scrutiny. The objective of this study was to conduct a meta-analysis assessing functional, oncologic, and perioperative outcomes of PN and radical nephrectomy (RN) in the specific case of larger renal tumors (≥cT1b). The primary endpoint was an overall analysis of cT1b and cT2 masses. The secondary endpoint was a sensitivity analysis for cT2 only. Overall, 21 case-control studies including 11204 patients (RN 8620; PN 2584) were deemed eligible and included in the analysis. Patients undergoing PN were younger (WMD -2.3 yr; P<0.001) and had smaller masses (WMD -0.65cm; *P*<0.001). Lower estimated blood loss was found for RN (WMD 102.6ml; p<0.001). There was a higher likelihood of postoperative complications for PN (RR 1.74, 95% CI 1.34-2.2; *P*<0.001). Pathology revealed a higher rate of malignant histology for the RN group (RR 0.97; *P*=0.02). PN was associated with better postoperative renal function, as shown by higher postoperative estimated glomerular filtration rate (eGFR; WMD 12.4ml/min; *P*<0.001), lower likelihood of postoperative onset of chronic kidney disease (RR 0.36; *P*<0.001), and lower decline in eGFR (WMD -8.6ml/min; *P*<0.001). The PN group had a lower likelihood of tumor recurrence (OR 0.6; *P*<0.001), cancer-specific mortality (OR 0.58; *P*=0.001), and all-cause mortality (OR 0.67; *P*=0.005). Four studies compared PN (n=212) to RN (n=1792) in the specific case of T2 tumors (>7cm). In this subset of patients, the estimated blood loss was higher for PN (WMD 107.6ml; p<0.001), as was the likelihood of complications (RR 2.0; p<0.001). Both the recurrence rate (RR 0.61; p=0.004) and cancer-specific mortality (RR 0.65; *P*=0.03) were lower for PN.
(continued on page 111)

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

Lenvatinib Approved by European Commission in Advanced RCC

The European Commission has stamped its approval on the use of Eisai's Kisplyx (lenvatinib) to treat advanced kidney cancer. The approval allows the drug's administration alongside everolimus (Novartis' Afinitor) in adults with advanced renal cell carcinoma (RCC) following one prior vascular endothelial growth factor (VEGF) targeted therapy.

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Kidney cancer awareness is represented by the orange ribbon.

Lenvatinib is an oral molecular trispecific targeted therapy with potent selectivity, says Eisai. The drug is already available in Europe under the tradename Lenvima in adults with progressive, locally advanced or metastatic differentiated (papillary, follicular, Hürthle cell) thyroid carcinoma, refractory to radioactive iodine.

Approval for RCC was based on data from a Phase 2 trial showing that the drug significantly extended progression-free survival (PFS) when added to treatment with everolimus; those given the combination regimen experienced a median PFS of 14.6 months versus 5.5 months for those taking everolimus alone.Hilary Glen, Consultant Medical Oncologist, Beatson West of Scotland Cancer Centre, Scotland, UK, said earlier this year: "The current outlook for people with this aggressive cancer is poor, and therefore the potential of lenvatinib is very exciting indeed".

Following the United States, Europe marks the second region where lenvatinib has been licensed for advanced RCC.

Incidence and Mortality of Kidney Cancer Tracked by NCI

The National Cancer Institute (NCI) has released new data on estimated new cases and deaths from renal cell (kidney and renal pelvis) cancer in the United States in 2016. The NCI estimates 62,700 new cases and 14,240 deaths.

FDA Approves Dosing Modification for Nivolumab

ROCKVILLE, MD—The Food and Drug Administration (FDA) has approved a modification to the nivolumab (Opdivo) dosage regimen for renal cell carcinoma, metastatic melanoma, and non-small cell lung cancer.

The new dosage regimen is for 240mg IV every 2 weeks until disease progression or intolerable toxicity for renal cell carcinoma, metastatic melanoma, and non-small cell lung cancer. This replaces the single-dose nivolumab 3mg/kg given intravenously (IV) every 2 weeks regimen.

The FDA approval was supported by population pharmacokinetic analyses and dose/exposure-response analyses demonstrating the comparability between the previously approved and the proposed new dosing regimen in terms of pharmacokinetics exposure, safety, and efficacy. The FDA concluded that overall exposure of 240mg every 2 weeks as a flat dose was similar (<6% difference) to 3mg/kg every 2 weeks. It was determined that these differences in exposure were not likely to have a clinically meaningful impact on safety and efficacy.

HIF-2 Inhibitors Studied as Novel Treatment Through a SPORE Grant

DALLAS—A new class of drugs, HIF-2 inhibitors, potentially could be investigated as a more effective and better tolerated approach than the standard of care drug sunitinib in treating kidney cancer, researchers with the Kidney Cancer Program at Harold C. Simmons Comprehensive Cancer Center have found. HIF-2 inhibitors, which grew out of research begun more than 20 years ago at UT Southwestern Medical Center, are effective by interfering with hypoxia inducible factor..

Investigators conducted a pre-clinical trial in mice transplanted with kidney cancer from over 20 patients and showed that the HIF-2 inhibitor PT2399 controlled cancer in half of the tumors, according to a study published in the journal *Nature*.

"This is a completely new treatment for kidney cancer. We want to make HIF-2 inhibitors available to patients and are currently carrying out clinical trials," said Dr. James Brugarolas, Director of the Kidney Cancer Program, who is leading an $11 million SPORE grant from the National Cancer Institute seeking to translate new discoveries into novel therapies for kidney cancer patients. Part of the SPORE grant, one of just two directly related to kidney cancer in the nation, is focused on further researching HIF-2 inhibitors.

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A Promising Hypothesis: Statins + Targeted Therapy May Improve Survival Outcomes in RCC

Rana R. McKay, MD
Assistant Professor of Medicine,
Harvard Medical School
Department of Medical Oncology
Dana-Farber Cancer Institute
Boston, Massachusetts

There are numerous examples of cross-disease benefits of different drugs. These agents have expanded the spectrum of therapy with unintended benefits in some setting. They have the potential to expand the treatment armamentarium of cancer targeting agents. New information is emerging on their use with targeted therapy. It raises a wide array of questions. Can stains synergistically work with targeted therapy to break a cascade of events and interrupt the signaling pathways of renal cell carcinoma? And when do hypothesis-generating studies begin to have translational and clinical impact?

It is still a controversy in search of a consensus: if statins are used in conjunction with targeted therapy, is there an improvement in survival for patients with renal cell carcinoma (RCC)? The controversy is far from settled, but it is a provocative and potentially important debate surging through the oncologic literature as new results have emerged to provide a sharper focus with which to address the conflicting findings. At this point, we are still waiting for prospective studies to address whether there is a clinical benefit to patients and translational and preclinical studies to understand the mechanism of action by which statins may exert their anti-neoplastic effects when combined with targeted therapy. These studies will help the field move beyond what at this point can be best described as a hypothesis-generating point of view. And the hypothesis from our recently published study[1] suggests that there is a clinical benefit to use of statins in patients with metastatic RCC, despite a considerable amount of evidence to the contrary.

Among the questions to be resolved:

- What are the possible mechanisms of action of statins and how do such mechanisms contribute to a hypothetical benefit?
- Does physiologic dosing of statins and the clinical pharmacokinetic properties of statins in humans exert anti-neoplastic effects?
- To what extent to these effects of statins, if any, translate into an improved survival for patients with localized RCC treated with surgery?
- What about survival outcomes in patients with metastatic RCC? If there is improved survival, could statins have a role as adjunct therapy? And which patient population with RCC should receive statin therapy?

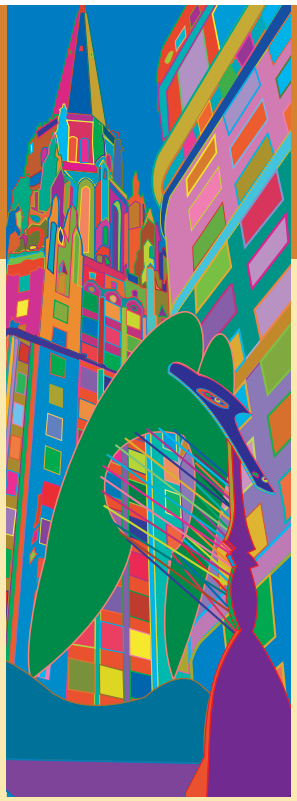
Our study navigated some of these issues in view of a growing body of evidence demonstrating the anti-neoplastic activity of statins; in contrast to some of the earlier studies, mainly conducted in patients with localized RCC, our pooled analysis of mRCC patients treated on phase 2 and 3 clinical trials examined the hypothesis in the modern therapy era. This is believed to be the first study to date that has evaluated the effect of statins in patients with mRCC treated with targeted therapy. By utilizing a large clinical trials database to investigate this effect, we planned to produce a study which could potentially impact the optimal treatment approaches in metastatic disease with drugs that are among the most commonly prescribed agents worldwide.

In planning this study we first considered substantial evidence from preclinical studies demonstrating the anti-neoplastic activity of statins. In 2003, for example, Chan et al[2] produced data from their study at the cellular level. In this report, statins were linked to blocking cell cycle progression, inducing apoptosis, and inhibiting cell-signaling pathways involved in tumor invasion and metastasis. There is also evidence from in vivo animal models further suggesting the anti-proliferative effects of statins.[3] A reduced risk of cancer-specific mortality has been documented by retrospective studies in humans involving prostate, colorectal and breast cancer.[4-6]

But a consensus on the issue has not emerged and skeptics can point to many studies showing no association between stain use and an improvement in survival in

Keywords: statins, targeted therapies, metastatic renal cell carcinoma, pharmacokinetic properties, survival outcomes.

Address for reprints and correspondence: Rana R. McKay, MD, Dana-Farber Cancer Institute, 450 Brookline Avenue, Boston, MA 02215. Email: Rana_McKay@dfci.harvard.edu



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RCC.[7-11] The majority of these studies, however, have been conducted in patients with localized disease and there have been limited studies in patients with metastatic RCC. As targeted therapy strategies have become the backbone of mRCC management in the modern era, there is a need to evaluate whether statins could be effective when combined with treatments to inhibit the vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) pathways.

Our pooled retrospective analysis involved mRCC patients treated on phase 2 and 3 clinical trials. We identified 4736 patients treated with sunitinib (n=1059), sorafenib (n=772), axitinib (n=896), temsirolimus (n=457), temsirolimus+interferon (IFN)-α (n=208), bevacizumab+temsirolimus (n=393), bevacizumab+IFN-α (n=391) or IFN-α (n=560), of whom 511 were statin users. Patient follow-up consisted of imaging assessment every 4 to 12 weeks until disease progression or withdrawal.

Overall, statin users demonstrated an improved overall survival (OS) compared to non-users (25.6 versus 18.9 months, adjusted hazard ratio [aHR] 0.801, 95% confidence interval [CI] 0.659-0.972, *P*=0.025). When stratified by therapy type, a benefit in OS was demonstrated in statin users compared to non-users in individuals receiving therapy targeting vascular endothelial growth factor (28.4 versus 22.2 months, aHR 0.749, 95% CI 0.584-0.961, *P*=0.023) or mammalian target of rapamycin (18.6 versus 14.0 months, aHR 0.657, 95% CI 0.445-0.972, *P*=0.035) but not in those receiving IFN-α (15.6 versus 14.8 months, aHR 1.292, 95% CI 0.703-2.275, *P*=0.410). Adverse events were similar between users and non-users.

First Study to Examine Statin Use in Metastatic RCC

As the largest database using prospectively collected clinical trials information to assess the impact of statin use in mRCC—and the first to address the effect of statins when combined with targeted therapy—this study is noteworthy for several reasons. It extends the findings from earlier studies; there are a limited number of studies concerning the effect of statin use on RCC development, including a case-control study of 500,000 veterans confirming the protective effect of statins.[12] In a smaller, population-based study, authors also confirmed a protective effect—but only in patients without hypertension.[11] There have been mixed results when statins have been used in studies following nephrectomy. Our study is reportedly the first of its kind to evaluate the effect of statins in mRCC.

Postoperative Outcomes With Statins and Preoperative Lipid Levels

Limited information is available on prognosis when statin users are compared with non-statin users following surgical treatment for RCC. The available studies have shown conflicting results. Given the substantial controversy in the literature, Haddad et al[13] evaluated the association of both statins and serum lipid parameters with RCC prognosis in patients treated for localized RCC. This recently published study is also a first in the literature in its own regard—demonstrating the association of triglycerides, LDL, and HDL cholesterol with outcomes in RCC.

In the Haddad study, a total of 850 patients who underwent surgery for localized renal cell carcinoma at the University of Texas Southwestern Medical Center from 2000 to 2012 were included. Use of statins, preoperative serum lipid profile, and comprehensive clinicopathologic features were retrospectively recorded.[13]

There were 342 statin users and 508 non-users. Median follow-up was 25.0 months. Statin users were older, had greater body mass index, and had worse performance status than non-users. Tumor pathologic characteristics were balanced between groups. Five-year recurrence free survival (RFS) was 77.9% for non-users compared with 87.6% for statin users (*P*=.004). After adjustment for clinicopathologic variables, statin use was independently associated with improved RFS (hazard ratio [HR] 0.54, 95% confidence interval [CI] 0.33-0.86, *P*=.011) and overall survival (HR 0.45, 95%CI 0.28-0.71, *P*=.001). In patients with available serum lipid parameters (n=193), 5-year RFS was 83.8% for patients with triglycerides <250 mg/dL compared with 33.3% for those with triglycerides >250 mg/dL (*P*<.0001). Elevated serum triglycerides (>250 mg/dL) was independently associated with worse RFS (HR 2.69, 95%CI 1.22-5.93, *P*=.015) on multivariate analysis.

Although there were some limitations to the Haddad et al study such as the retrospective design and a lack of confirmation as to the duration of statin use, the analysis confirmed that statins remained protective—significantly improving recurrence free survival—even after the exclusion of patients who had started statin therapy after surgery. Although the analysis of lipid profiles was limited to a quarter of patients whose preoperative lipid profiles were obtainable, the benefits of statin use emerged even when the analysis was restricted to patients with available serum lipid parameter data.

This report also offered further insights into the potential role of triglyceride levels as a prognostic factor in localized RCC. Several studies had previously demonstrated an increased risk of cancer in patients with elevated triglycerides, but none have done so in RCC patients. Though these results require validation in larger dataset, a novel finding here was the detrimental association of elevated serum triglyceride levels with RCC prognosis after surgery. However, no independent association was found between total cholesterol levels and oncologic outcomes in the Haddad report. The prognostic significance of lipid levels in patients with metastatic disease is unknown.

Long-term Use of Stains in RCC: Registry Data Dispute Benefit

As a reminder that the use of statins in RCC remains a cautionary tale, a Danish study[14] used a nationwide population-based, case-control design to evaluate the hypothesis that stain use is associated with a reduced RCC risk in patients with localized disease.

This study covered a 10-year period based on all histologically verified cases of RCC (n=4606) matched 1:10 to cancer-free controls. The adjusted OR for RCC associated with long-term use of statins was 1.06 (95% CI, 0.91-1.23). Analyses stratified by duration of statin use, type of statin, and patient characteristics all yielded ORs close to unity, except for a slightly increased OR for RCC associated with long-term statin use among women (OR: 1.25; 95% CI, 0.96-1.62). The main limitation of this study was the lack of information on lifestyle factors, notably obesity, which may have biased the risk estimates upward. The study did not support a chemopreventive effect of long-term statin use against RCC. The marginally increased and statistically insignificant risk estimates can readily be interpreted as a null finding, considering the lack of control for obesity and other lifestyle risk factors.

If one were looking for a high-quality assessment, the Danish study seems to offer compelling evidence for its null finding. Pottegard suggest that in Denmark the group is uniquely positioned to perform a population-based study with almost complete population coverage since almost all health care service is administered by the publish health system. RCC cases were identified from the Danish Cancer Registry which has accurate and virtually complete registration of incident cancer in the country, with up to 18 years of drug exposure history. However, one of the limitations of the study remains whether the results in a Danish population could be extrapolated to patients in other countries.

"One of the key questions arising from the numerous studies on statin use, particularly in the reports finding a favorable association, is whether the anti-cancer effects of statins reported in preclinical studies can be extended to the clinical arena."

Generating a Hypothesis on Why Statins May Be of Benefit

One of the key questions arising from the numerous studies on statin use, particularly in the reports finding a favorable association, is whether the anti-cancer effects of statins reported in preclinical studies can be extended to the clinical arena. In this regard, numerous hypotheses have been proposed on the possible mechanism that could account for anti-tumor properties. One study, for example, suggests that a consequence of statin inhibition of the cholesterol pathway is reduced production of isoprenoid intermediaries including farnesyl pyrophosphate and phosphate.[15]

This mechanism has also been the focus of another study.[16] Farnesyl pyrophosphate and geranylgeranyl phosphate are involved in the post-translational prenylation of small GTPases such as Ras and Rho. These small signaling proteins have important roles in cell growth, differentiation and cancer. Still other studies have also postulated on mechanisms that may be implicated. One report by Woodward et al demonstrated that fluvastatin potently induced apoptosis in RCC cells in vitro. The apoptosis in this case was mediated by inhibition of the mammalian target of rapamycin (mTOR) pathway.[17]

Blanco-Colio et al investigated yet another possibility: the role of adipokines.[18] White adipose tissue collectively referred to as either subcutaneous or visceral adipose tissue is responsible for the secretion of an array of signaling molecules, termed adipokines. These adipokines function as classic circulating hormones to communicate with other organs including brain, liver, muscle, the immune system, and adipose tissue itself. Statins are known to alter the serum concentrations of adipokines, a possible mediating effect on this pathway that may result in an anti-cancer effect.

Identifying Molecular Mechanisms, Hypothetical Synergistic Interactions

Efforts to pinpoint the possible molecular mechanisms involved with statin use have also explored other avenues. A study by Fang et al[19] has shown that simvastatin exerted an anti-tumor effect by suppressing interleukin-6-induced phosphorylation of JAK2 and STAT3. A report that could be considered related to this finding came from Marotta et al: they found that the IL-6/JAK2/Stat3 pathway was preferentially active in CD44+CD24- breast cancer cells compared with other tumor cell types, and inhibition of JAK2 decreased their number and blocked growth of xenografts.[20] Their results highlight the differences between distinct breast cancer cell types and identify targets such as JAK2 and Stat3 that may lead to more specific and effective breast cancer therapies.

Our review of the literature also identified additional reports on a possible synergistic interaction between statins and VEGF or mTOR-targeted agents. The addition of lovastatin to VEGF inhibitor therapy resulted in more robust AKT inhibition in mesothelioma cells than was seen with either agent alone.[21] And everolimus and fluvastatin could act synergistically to interfere with the AKT pathway in leukemia cells.[22] Our study demonstrated an overall survival benefit in statin users receiving either VEGF or mTOR-targeted therapy.

Pharmacokinetic Properties of Statins: A Delicate Balance in the Liver

If the hypothesis-generating results from our study can be further replicated and verified, a key question is what strategies would be appropriate to optimize their pharmacokinetic properties. While nanomolar plasma concentrations have been used to treat lipid disorders, non-physiologic concentrations are often utilized to elicit robust anti-cancer responses.[23] For statins to achieve anti-neoplastic effects, they ostensibly should be able to enter extra-hepatic malignant cells. One problem to this theory, however, is that extensive first-pass metabolism and high levels of protein binding limit systemic bioavailability.[24]

(continued on page 96)

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.

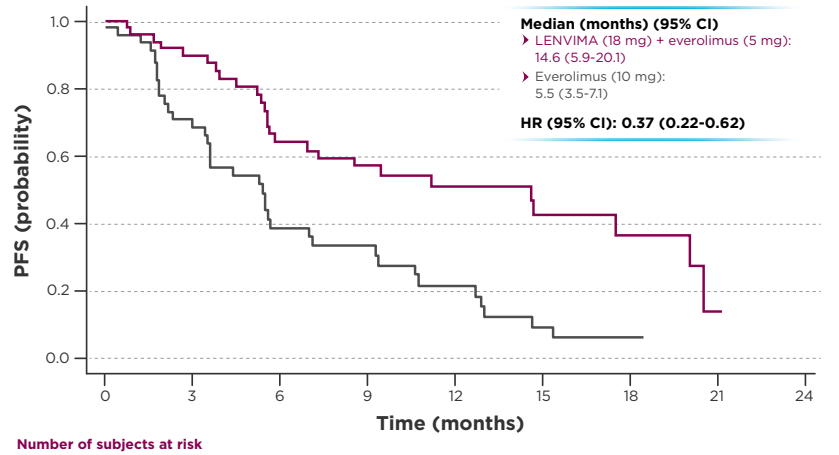
Important Safety Information

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

	LENVIMA 24 mg N=261		Placebo N=131	
Adverse Reaction	**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

	LENVIMA 18 mg + Everolimus 5 mg (N=62)		Everolimus 10 mg (N=50)	
System Organ Class Preferred Term	**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.

Eisai

(continued from page 89)

Still another issue considered potentially problematic is the delicate balance between statin lipophilicity and hepatoselectivity. Some statins may potentially achieve greater anti-neoplastic effects depending on their metabolism in this respect. In our study the most frequently used statins were lipophilic—simvastatin, atorvastatin, and fluvastatin. They enter hepatocytes and extra-hepatic cells via non-selective passive diffusion. The hydrophilic statins, however, including pravastatin and rosuvastatin, enter hepatocytes through an active transporter in liver tissue and are more hepatoselective and achieve limited systemic drug levels.

These mechanisms, namely, that statins function primarily in the liver, suggest that the beneficial effects of these drugs are achieved through inhibition of liver metastasis development and progression. Statin users in our cohort had improved overall survival compared to nonusers even after adjustment for the presence of liver metastases. Thus, it may be that the anti-cancer effects of drugs used for non-cancer indications could be a worthwhile approach. These cross-disease benefits at the least generate a new hypothesis and a potentially promising avenue of therapy.

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Consulting With the Author

'Take-Home' Messages: What's the Status of Statin Use in RCC?

In this interview, Rana R. McKay, MD, discusses the relative merits, implications and potential impact of the use of statins in renal cell carcinoma (RCC). She is a co-author of a recent study in the European Journal of Cancer on the use of statins with targeted therapies in metastatic RCC. Dr McKay provides a concise but revealing summary of the status of statin use in RCC.

Q. Although controversial, it seems that the prevailing trend suggests statin use *is* associated with improved survival in kidney cancer. But there are a considerable number of studies suggesting the opposite. What is your view of this discrepancy?

Dr McKay: The issue is that most of the studies that are out there either look at risk of RCC development or risk of progression in patients with localized disease. There are very limited studies actually looking at outcomes of patients with metastatic disease receiving statins. Our analysis is the largest and most robust analysis to date in the metastatic disease setting. The studies in patients with localized disease have been mixed and are worth highlighting. Also, all these studies are retrospective and there are no prospective randomized studies to actually "prove" that statin use does indeed impact outcomes for patients with RCC. Our data are hypothesis-generating for further

exploring this clinical question in a prospective manner in patients.

Q. A trend toward improved survival appears to be evident in both metastatic RCC and localized RCC, correct?

Dr McKay: Yes that is correct. While the overwhelming majority of studies have been conducted in the localized disease setting, there is data documenting a positive association between statin use and survival in patients with both localized disease and metastatic disease.

Q. Is your study population-based or do we still need that type of study to prove that there is benefit? Are there any plans to do a prospective, randomized trial?

Dr McKay: Our study was a retrospective study of prospectively collected data from a clinical trials database. The database included over 4000 patients and is a robust tool for answering clinical questions. Given the retrospective nature of our study, these data are hypothesis-generating and ultimately need to be validated prospectively in patients, potentially through a randomized clinical trial. However, there are significant barriers to conducting such a trial in this population including funding, heterogeneous RCC patient population, and the rapidly evolving treatment landscape for patient with metastatic RCC. Thus, our study, despite its retrospective design, provides the most robust data supporting the benefit of statins in mRCC and fills a void of missing knowledge in the field given the lack of prospective data to guide clinical decision making in patients. i

Q. To what extent are distinctions between stains based on lipophilicity or hepatoselectivity important? Is it fair to say that simvastatin, atorvastatin and rosuvastain yield more benefit because they are less hepatoselective?

Dr McKay: It is critical to pay attention to the pharmacokinetic properties of statins ad potential anti-neoplastic effects. There are several different statins currently prescribed today, each with a differing pharmacokinetic profile that impacts drug bioavailability, tissue site of action, and drug potency. These factors are important to consider when thinking about the potential role of statins as anti-neoplastic agents.

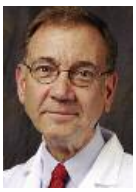
Q. What do we need now to take your hypothesis-generating results to the next stage? What parameters would you like to see in a future study?

Dr McKay: There are two paths for next steps from our work. One is to further investigated the mechanism underlying the positive benefit seen with statins in combination with VEGF and mTOR targeted therapies via preclinical and translational studies. These studies can potentially help identify the most optimal statin and drug combination to investigate prospectively. The second path from this work is to attempt to conduct a randomized controlled trial in the metastatic setting. Questions that will need to be considered for such a trial is which combination of therapies to consider including drug type and dosing and which patient population including prior treatments, underlying histology, and history of dyslipidemia or prior statin use.

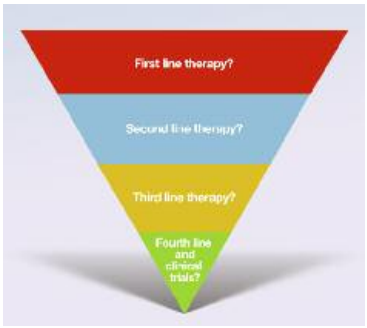
Q. In a patient with no history of hypercholesterolemia but who has localized or metastatic RCC, is there any justification—on a purely empirical or anecdotal basis—to start statin therapy? Or is the risk/benefit ratio not really determined?

Dr McKay: In a patient without hypercholesterolemia the decision would be empirical and our study does not support the use of statins in this setting. Though the risk/benefit is likely low, as can be extrapolated from our study which demonstrated similar adverse events between statin users and non-users, there are reports of increased hepatotoxicity when statins are used in combination with VEGF targeted therapy. Additionally, whether a tangible benefit would be observed is unknown. As such, empiric treatment with statins in patients with mRCC without hypercholesterolemia or other reason to warrant statin use is not recommended based on our study as we did not test this clinical question. KCJ

Deconstructing the Treatment Algorithm: What Is the Current Thinking on the Decision Tree?



In this interview, ***Nicholas J. Vogelzang, MD****, addresses a wide range of issues, controversies, confusion, and consensus as ongoing pivotal trials redefine the relative merits of sequential therapies in metastatic renal cell carcinoma. Recognizing that a paper he co-authored earlier this year on the topic is already out of date, Dr Vogelzang nevertheless reviews how the US Oncology Network is seeking to join "real-world" clinical practice with emerging trial data, a daunting task in a rapidly evolving treatment landscape. Dr Vogelzang is Vice Chair of the SWOG GU Committee and Chair GU Committee of US Oncology Research, Comprehensive Cancer Centers of Nevada, Las Vegas, Nevada.*



Q. What is the US Oncology Network (USON) and why is it important to a discussion on sequential therapy in metastatic renal cell carcinoma (RCC)?

Dr Vogelzang: USON is the largest community-based network of oncology providers in the country. The members of the Genitourinary Committee and the rest of USON treat relatively high volumes of mRCC patients. Earlier this year, we published an article outlining our thoughts on sequential therapy of RCC. This discussion presents a framework upon which to evaluate new agents and how evidence is to be considered for their efficacy. Our experience is enhanced by the "real-world data" analyses that occur within our group. These "real-world data" are critically important to demonstrate the external validity of the trial data upon which our guidelines are based.

Q. Since the publication of your study in the *Journal of Kidney Cancer and VHL* earlier this year,[1] which included a treatment algorithm, how has the landscape changed, particularly with regard to frontline therapy?

Dr Vogelzang: The landscape is changing so rapidly that much of the information in our article is already outdated. That's why it is important in the discussion right here to update some of the opinions expressed and revisit the approaches in view of new approvals within the last six months.

Q. So what is key to how first-line therapy is changing?

Dr Vogelzang: I think the algorithm for first line is going to change when we see results from the CABOSUN trial, which is cabozantinib vs sunitinib. It's a randomized, phase 2 study in intermediate and poor risk patients. As a phase 2 it is not powered to change practice but certainly will affect practice and clinical trial decision making. The biggest problem was that it did not include good-risk patients. They were excluded so that the end point could be achieved sooner. Likewise, the poor-risk patients were included because they have not benefited nearly as much from TKI therapy as good and intermediate risk patients.. Thus CABOSUN is not generalizable to all RCC patients. The CABOSUN data will be fully reported at ESMO but per the press release showed a PSF advantage for cabometyx.

In addition to the CABOSUN data there are at least four phase 3 trials underway or completed in first line RCC. These are

1. Atezolizumab plus bevacizumab vs sunitinib
2. Nivolumab plus ipilimumab vs sunitinib
3. Pembrolizumab plus axitinib vs sunitinib
4. Pembrolizumab plus lenvatinib vs lenvatinib plus everolimus vs sunitinib
5. Avelumab plus axitinib vs sunitinib

These trial designs make it clear that most clinical trialists are assuming that an immune-check point inhibitor (IO) plus a potent TKI like axitinib or lenvatinib or plus ipilumab will be shown superior to sunitinib within the next 1-3 years in first line therapy of RCC.

Q. In reviewing all of the options identified by guidelines from widely recognized groups such as the National Comprehensive Cancer Network, you have pointed to various factors that make the evaluation of different classes diffi-

cult. To what extent are patients actually receiving the therapy they may need?

Dr Vogelzang: Despite the overlapping survival curves of pazopanib and sunitinib in the COMPARZ trial, there is variability in their toxicity and efficacy profiles. So they are not readily interchangeable. Assuming that a patient has progressed on either agent we do not know the efficacy of the alternate agent. Choice of second-line therapy and beyond becomes then very complex, as many agents are available, including, nivolumab, cabozantinib, lenvatinib, axitinib, everolimus, sorafenib as well as either sunitinib or pazopanib. To further complicate the picture, patients often become sicker as the disease progresses, forcing physicians to incorporate other considerations such as performance status, comorbidities, and preferences regarding end-of-life care into decisions about treatment options. In fact, evidence suggests that only about 50% of patients in the United States receive second-line therapy as opposed to best supportive care.[2] Italian analyses similarly showed that approximately 50% of patients received second-line therapy, and only 13% of patients received third-line therapy.[3,4]

Q. Where does that leave high-dose interleukin-2 therapy?

Dr Vogelzang: For patients who are young, otherwise healthy, and wish to be maximally aggressive, high-dose IL-2 can be considered. In one study, treatment with high-dose IL-2 achieved objective responses in 20% of patients, with complete responses in 9%.[5] To date, no other agent approved in the treatment of mRCC has achieved similar complete response results. However, the intensity and toxicity of treatment are quite high. There is a commentary by a patient who presents his story online[6] and his name is Dave deBronkart. He talks about how his disease was cured by his search of the Internet, identification of IL-2 as an option, and active pursuit of it after his physicians failed to inform him about its availability. Patients should be able to similarly weigh the pros and cons of the various treatment options. However, as discussed, few receive IL-2 in practice.

Q. Should we be paying more attention to biomarkers, factors that could lead to better patient selection for IL-2?

Dr Vogelzang: It may be. But no one really knows when IL-2 will be of benefit. Intermediate-risk and good-risk patients should always be considered for IL-2 but patients over 60 can rarely tolerate IL-2.

Q. What deters clinicians from considering it as frequently as should be the case?

Dr Vogelzang: Certainly the side effects and the fact that patients need to receive it in the hospital. It requires ICU care. It's cumbersome. I do not do it. If I need to, I send the patient to one of my partners who will administer it in the hospital.

Q. Let's move on to second-line therapy and the options available. There is a lot of debate in this setting and strategies are competing with one another.

Dr Vogelzang: It is a significantly volatile area. There are so many studies going on first line that it is hard to imagine what will be the second line therapy when the first line trials start reporting out. The area is evolving so quickly that the article we published earlier this year on sequential therapy is already out of date.

Q. Do you have any perspectives as to how all of this activity will begin to shake out in terms of treatment imperatives or new thinking?

"The era of monotherapy is ending. Lenvatinib and everolimus were the first approved combination by the FDA. That was the beginning of the end of single agent therapy. It is not widely used in second line but it is an approved combination. The whole pattern of single-agent therapy is being disrupted."

Dr Vogelzang: It will largely depend on what study is the first to report. The first one likely to report is the Genentech trial—atezolizumab and bevacizumab versus sunitinib but the nivolumab plus ipilimumab may be also first to report. If both those trials trump sunitinib the second line space will include all the TKI's (cabozantinib, lenvatinib plus everolimus, axitinib, sorafenib, sunitinib or pazopanib). Since cabozantinib, sunitinib, lenvatinib plus everolimus and axitinib have all demonstrated superiority over everolimus in phase 2/3 trials, I believe it is that those 4 regimens will likely fight for the second line space. Given the striking survival results of cabozantinib against everolimus in a phase 3 trial and the results of CABOSUN, cabozantinib is likely to be chosen as the second line therapy after failure of an IO agent. Third line is likely to go to the lenvatinib plus everolimus combination leaving 4th line to our long term friends sunitinib, pazopanib and axitinib. Clearly we are going to need clinical trials to sort this out.

Q. When we talk about sequential therapy now, aren't we really talking about sequential combinations?

Dr Vogelzang: The era of monotherapy is ending. Lenvatinib and everolimus were the first approved combination by the FDA. That was the beginning of the end of single agent therapy. It is not widely used in second line but it is an approved combination. The whole pattern of single-agent therapy is being disrupted.

Q. You and your co-authors discussed "real-world" practice versus a more evidence-based approach generally associated with academic centers. Is it possible to reconcile

these "real-world" approaches that may differ from the clinical trial strategies, particularly in view of the fact that in the so-called "real world" patients may not always be eligible for a clinical trial?

Dr Vogelzang: Not yet. Let's take as an example a patient who comes in and there is no clinical trial available for him or her. Everyone still has to use either sunitinib or pazopanib as first line. I recently enrolled my first patient on the avelumab/axitinib versus sunitinib combination. I screen-failed four other patients who could not get into the trial for any number of reasons—their tumors were too small, they had too many co-morbidities etc. In all of these four patients, I put them on pazopanib or sunitinib. However when the front line IO trials report out and the FDA approves them as 1st line combinations our former first line drugs may be relegated to 3rd or 4th line!

Q. Is it fair to say we have two standards of care, one in the community setting and the other where clinical trials are available?

Dr Vogelzang: In the community setting, we either have access to the clinical trials, the clinical trials are too restrictive or the patients don't want to bother with the clinical trials. But even in the academic setting, the same problem is apparent: you may have a trial, and initially it looks great, but 60% of the patients are not eligible. You can't get them into the trial. Only when the FDA approves the combination can you treat them with the combination off of the trial.

"We predict that there will be extensive study of combinations of IO agents such as nivolumab (now approved as a monotherapy second line) with sunitinib, pazopanib, or ipilimumab. Although combinations have proven difficult in RCC, the toxicity profile and response of nivolumab may make its use in combination a viable option."

Q. What are some of the central issues in terms of reconciling what's happening in the so-called real world versus the clinical trial setting?

Dr Vogelzang: The use of data generated in clinical practice to inform treatment considerations has not been fully realized. A recent article compared patients included in the pivotal clinical trials with those treated with sunitinib, sorafenib, pazopanib, and temsirolimus in the community. The "real world" cohort was part of a joint academic community registry.[7] According to our paper, overall, 39% of the registry patients would not have met the inclusion and/or exclusion criteria for the relevant pivotal trial used to approve the drug that they received. As an example, among the 438 community patients, those who received tyrosine kinase inhibitors were more likely to have poor-risk disease (7.4% vs 2.9%, $P<0.001$) and less likely to have favorable disease (30.1% vs43.8%, $P<0.001$) when compared with those in the trials. Those treated with temsirolimus were less likely to have poor-risk disease (10.2% vs 69.4%) when compared with those in the trial, despite poor risk being the indication for the use of the agent.

Q. Are the results from your experience in the USON group very much different from the clinical trials experience?

Dr Vogelzang: These findings beg the question of whether those patients treated in the community have similar outcomes and toxicity profiles compared with those who participate in the clinical trials used to approve a given agent. An abstract presented at the ASCO Genitourinary Meeting in January 2016 described outcomes of USON patients treated with pazopanib or sunitinib in the first-line.[8] Median PFS was 9.3 months with pazopanib and 8.3 months with sunitinib when compared with 11 and 11.1 months in the pivotal trials. Median OS was also similar between the two agents at 22.3 and 26.3 months in the USON retrospective cohorts, respectively, when compared with 22.9 and 26.4 months in the pivotal trials. These results are reassuring in that the outcomes are not dramatically different overall, or by agent comparing community to academic sites. In the USON retrospective series, adverse events (any grade), including anorexia, skin toxicity, and stomatitis, were significantly less common among pazopanib-treated patients ($P<0.05$), whereas diarrhea, hypertension, nausea, and vomiting were significantly less common with sunitinib ($P<0.05$). Patients treated with sunitinib also appeared to have higher incidence of headache and pain in an extremity although the difference was not statistically significant.

Q. Given what we've seen recently with the new trials, what does your group envision as we move further into the treatment landscape?

Dr Vogelzang: We predict that there will be extensive study of combinations of IO agents such as nivolumab (now approved as a monotherapy second line) with, sunitinib, pazopanib, or ipilimumab.[9] Although combinations have proven difficult in RCC, the toxicity profile and response of nivolumab may make its use in combination a viable option. Furthermore community oncologists are familiar with those single agents and some of the combinations like nivolu-mab and ipilimumab.

Over the next few years, the role of checkpoint inhibitors will evolve further as other agents are approved, as has occurred with TKI and mTOR inhibitors, and as first-line trials read out. Combinations of checkpoint inhibitors and anti-angiogenic agents will continue to be studied although early trials have shown significant toxicity.

Q. How can groups like USON and other entities engage in data-mining from their system to better delineate the role of available agents?

Dr Vogelzang: Beyond the introduction of new agents, the utility of data and informatics to drive care is promising. Groups such as the USON are establishing systems and approaches that will leverage data from electronic health records, genomic analyses, and other systems to assess risk, improve understanding of the optimal role for specific agents, and provide clinical decision support to enable personalized recommendations. Real-world data could be used to update the analyses and help to further define the roles of available agents. It is likely that the output would be more nuanced and complex than prior approaches; however, it could be supported with available systems.

Q. There was initial excitement over the prospect of autologous dendritic cell immunotherapy in kidney cancer. But we have not heard much from this sector to cheer about at recent meetings or much that is forthcoming from the companies investigating this modality. Why is that?

Dr Vogelzang: The results have been somewhat mixed. The initial optimism about autologous vaccines still needs confirmation from phase 3 trials and we are awaiting results, for example, from the ADAPT trial of autologous dendritic cell immunotherapy. The agent, AGS-003 is being given in conjunction with sunitinib in newly diagnosed patients to assess the effect of a combined approach of TKI and immunotherapy. Data from the phase 3 IMPRINT trial have not been encouraging. Results presented last year at the European Cancer Congress on the use of a vaccine in combination with sunitinib indicated that the combination did not meet the primary endpoint of an extension in overall survival when compared with sunitinib alone.

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Updated Long-term Responders With Metastatic Clear Cell Kidney Cancer to Treatment With AGS-003, an Autologous Dendritic Cell-based Immunotherapy, in Combination With Sunitinib


Gautam Jha, MD


Mark DeBenedette, PhD


Lee F. Allen, MD, PhD


Shawn M Leland, PharmD, RPh


Arkadiusz Z. Dudek, MD, PhD

Gautam Jha, MD[1], Mark DeBenedette, PhD[2], Lee F. Allen, MD, PhD[2], Shawn M. Leland, PharmD, RPh[2], and Arkadiusz Z. Dudek, MD, PhD[3]
[1]University of Minnesota, Minneapolis, MN, USA
[2]Argos Therapeutics, Durham, NC, USA
[3]University of Illinois, Chicago, IL, USA

Introduction

Metastatic renal cell cancer (mRCC) is an immunologically responsive disease with only 5% of patients achieving durable remissions with high dose interleukin-2 therapy.[1,2] However because of the severe and frequently intolerable side effects of this intense therapy, its use has become restricted to patients with robust organ function and administration is centered mainly at experienced major treatment centers. Over the past decade, therapies targeting the vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) pathways have demonstrated clinical benefit with clinical responses and improvement in survival, which have largely replaced interleukin-2 outside of major academic centers; however durable disease control still remains exceptionally rare.[3,4] More recently the immuno-oncology agent, nivolumab,[5] the first immune checkpoint inhibitor, was approved for patients with mRCC who have progressed on first line therapy.[6-8]

AGS-003 is an individualized, autologous dendritic cell (DC)-based immunotherapy that uses autologous tumor RNA as the source of tumor antigens, and was designed to induce an adaptive immune response specifically directed to a patient's tumor antigens. It involves *ex-vivo* electroporation of autologous DCs harvested via leukapheresis, with both amplified autologous renal tumor RNA containing neoantigens and synthetic CD40 Ligand (CD40L) RNA providing a co-stimulatory factor; this was designed to provide for tumor-specific antigen presentation by these DCs to the patient's immune system. By capturing the array of known, unknown, and mutated antigens present in an individual patient's specific cancer, AGS-003 is designed to elicit the broadest, individualized antitumor immune response.

AGS-003 was administered as first-line treatment in combination with sunitinib in a Phase II study (AGS-003-006) to patients with intermediate or poor risk mRCC, which led to increases in progression free survival (PFS) and overall survival (OS) relative to published benchmark data.[9-12] Importantly, patients in this study were shown to exhibit immune responses post-treatment, as reflected by an increase in the number of CD28+CD45RA- effector/memory cytotoxic T cell (CTLs) after 5 doses of AGS-003 compared to Baseline. Further, this change in immune response from Baseline was importantly correlated with improved survival in subjects who received 5 or more doses of AGS-003 (n=14); i.e., who completed the Induction Phase. Moreover, the change in the measured immune response was shown to be a prognostic indicator for clinical outcome, where those patients with a smaller change in the measured immune response following AGS-003 had a shorter OS compared to those patients who had a greater change in the measured immune response who had a longer OS.[9]

Here we provided an update on two unusual cases from this Phase 2 study with intermediate risk mRCC, who obtained long term control of metastatic disease that is remarkably still ongoing nearly seven years after initiation of AGS-003 therapy. Further for one of these patients, longitudinal immune response data were available that demonstrated the important induction of CD28+ CD45RA- effector/memory CTLs, which have been asso-

Keywords: renal cell cancer, immunotherapy, dendritic cell therapy, cytotoxic T lymphocytes, AGS-003, sunitinib, CD28+CD45RA- effector/memory CTLs, neoantigens, immuno-oncology, personalized medicine

Trial Registry: The two patients in this case study were enrolled in phase II clinical trial NCT00678119, registered 05/14/2008 and later were continued on rollover protocols with continued response to therapy - NCT01482949, registered 11/17/2011.

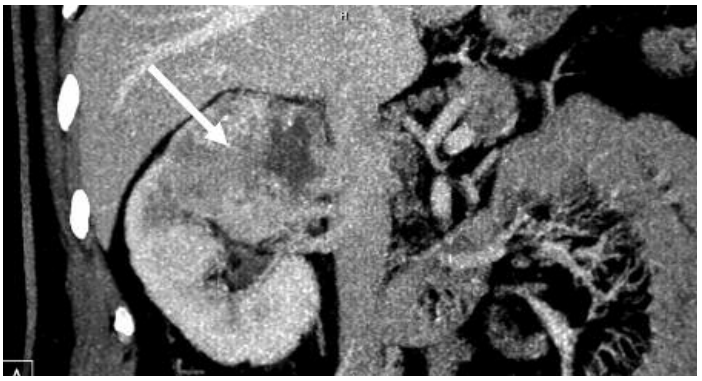

Figure 1A. Right renal primary on CTA- Case 1

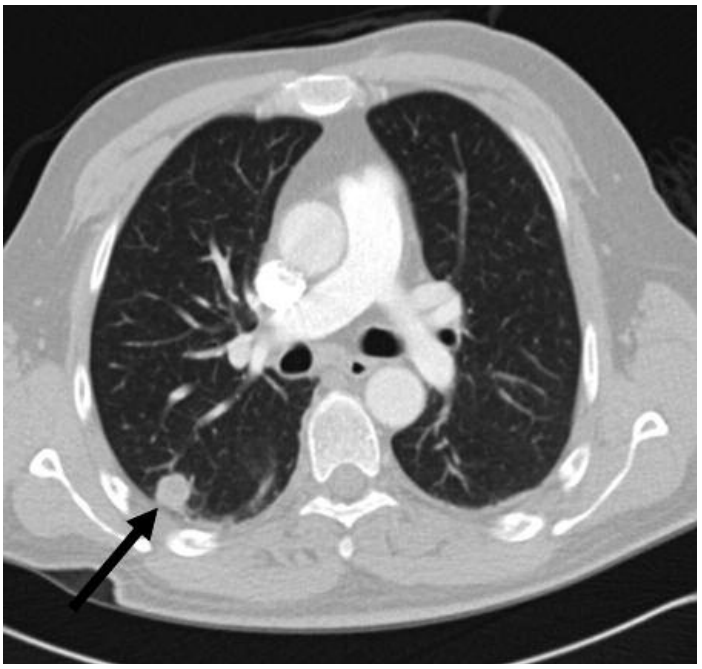

Figure 1B. Lung metastasis at presentation- Case 1

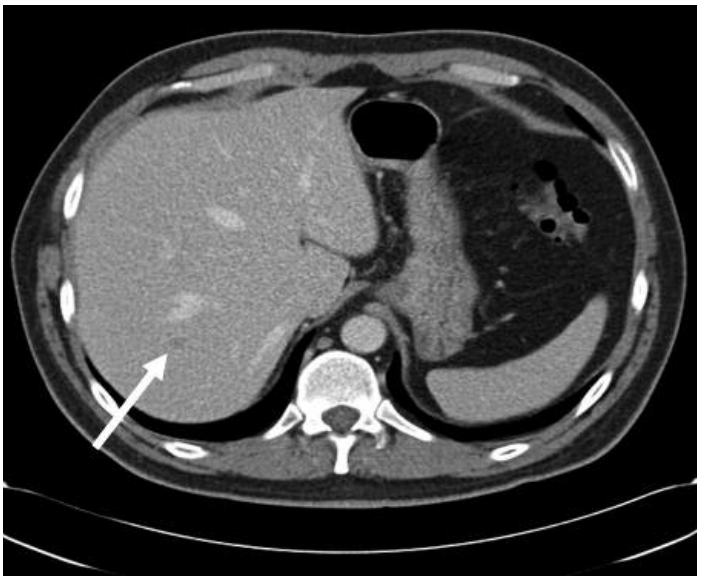

Figure 1C. Liver metastasis at presentation- Case 1

ciated with improved survival. In addition, the presence of naïve central memory-like CTLs, that also have effector function, were demonstrated in this subject during the Booster Phase of AGS-003 treatment.

Case Presentations

Case 1: A 44-year-old male with no significant past medical history who was evaluated for right flank pain and found to have an 8 x 8.4 x 9 cm mass in the right kidney (**Figure 1A**) consistent with clear cell RCC. Staging work up revealed multiple pulmonary nodules (**Figure 1B**), and a liver nodule (**Figure 1C**) in segment 7 consistent with metastatic disease. This patient required treatment initiation within a year of diagnosis, one of the six Heng prognostic criteria,[11] and therefore had intermediate risk disease (**Table**). After reviewing treatment alternatives, the patient was enrolled in the AGS-003-006 Phase 2 trial to receive combination treatment with AGS-003 immunotherapy and sunitinib.

The patient had a cytoreductive right nephrectomy to reduce tumor burden, which also provided the tumor sample to use for AGS-003 preparation. His post-operative course was complicated by bilateral deep vein thrombosis, renal insufficiency, pneumonia and depression. Per protocol, the patient was started on sunitinib therapy (50 mg orally once daily, 4 weeks on and 2 weeks off) although post-operative complications delayed the start of therapy to 10 weeks after surgery. After the first cycle of single-agent sunitinib, the patient received it in combination with AGS-003 immunotherapy per protocol (Induction Phase- every 3 weeks for five doses; Booster Phase- every 12 weeks).[9]

This patient had a partial response within the first year of therapy, and the dose of sunitinib was decreased to 37.25 mg on the same schedule due to marked fatigue.

Table. Heng Prognostic Criteria for the Two Patients with mRCC[1]

	KPS PS	Time to Treatment Post-diagnosis	Hemoglobin	Osmolality	Neutrophil count	Platelet count	Total Number of Risk Factors
Case 1	80	< 1 year	15	9.4	5.2	227	1
Case 2	70	< 1 year	13.4	9.6	6.1	221	2

[1]Per Heng criteria[11]

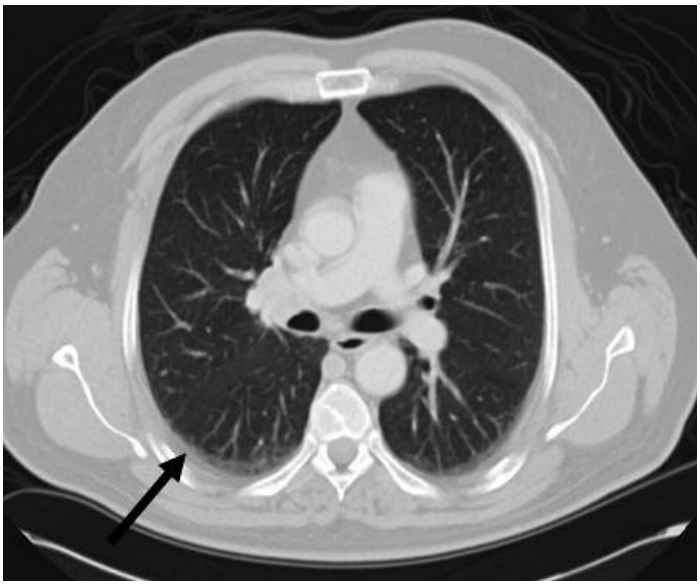

Figure 2A. Stable lung metastasis after treatment for nearly 7 years- Case- 1

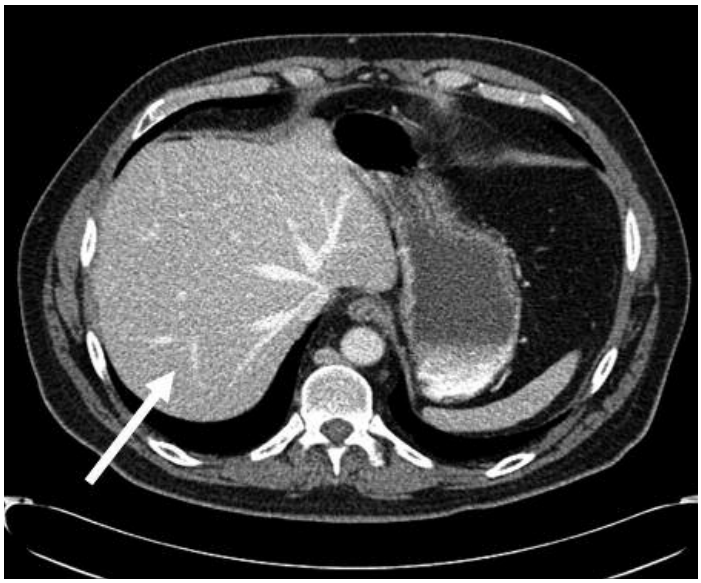

Figure 2B. Complete resolution of liver metastasis after treatment for nearly 7 years- Case 1

Over the next year, he had a near complete resolution of all lesions. While on therapy, the patient developed an ST elevation myocardial infarction (STEMI) nearly 5 years out from the start of treatment with a drop in ejection fraction (EF) to 35%. The patient's sunitinib had to be held due to the STEMI for 10 weeks, until his left ventricular EF improved to about 44%; treatment with AGS-003 booster doses continued during this period. With near complete response of his mRCC, AGS-003 booster dosing continued. Six months after STEMI sunitnib was held again for 8 weeks non-healing ulcer.

Nearly 6 years after start of therapy, the patient was noted to have progression in one of the pulmonary nodules. His sunitinib dose was then increased to 50 mg on the standard schedule, which he tolerated without difficulty. He had stable disease for 6 months, but again had progression in the same pulmonary nodule. After 7 years of therapy with standard of care sunitinib in combination with AGS-003 immunotherapy, the patient continues on therapy with disease limited to a couple of nodules in the lungs and non-enlarged mediastinal nodes (**Figure 2A**, **Figure 2B**).

"AGS-003 when administered along with sunitinib as frontline therapy is very well tolerated without any significant additional side effects over single agent sunitinib therapy and can be continuously administered for period of years without significant treatment burden to the patients."

Given the correlation of the induction of memory T cells with OS previously reported in Phase 2 patients who received 5 or more doses of AGS-003 in combination with sunitinib,[9] it was important to map the immune response in this long-term responder over the course of treatment using data spanning 36 months of treatment as discussed below.

Case 2: A 56 year old female, chronic active smoker with an over 30 pack-year history of smoking, hypertension, diabetes, morbid obesity, obstructive sleep apnea, coronary artery disease and non-ST elevation myocardial infarction (status post per cutaneous angioplasty and drug eluting stent placement 6 months prior to presentation), who presented with persistent left shoulder pain. Initial management with physical therapy, pain medications and intraarticular steroid injections did not provide any relief, and the patient was referred to an orthopedic surgeon. Further evaluation revealed a large destructive neoplastic lesion involving the left proximal humerus (**Figure 3A**).

Staging studies found a 3.1 x 2.7 x 4.3 centimeter (cm) mass in the upper pole of left kidney (**Figure 3B**) and a 2.7 x 2.2 x 3.3 cm lesion near the right renal pelvis (**Figure 3C**). The patient had a total en-block resection of 14 cm of the humerus containing the metastases, and prosthetic reconstruction. Pathology confirmed a very high grade, poorly differentiated adenocarcinoma that extended to the marrow with positive superior, lateral, medial and anterior resection margins. The patient was then treated with external beam radiation therapy and received 30 gray in 10 fractions for local disease control to the left humerus.

This patient had two Heng prognostic risk factors, i.e., performance status and less than one year from diagnosis to the start of treatment, and was classified as intermediate risk mRCC (**Table**).[11] Because of her cardiovascular disease and recent myocardial infarction, the patient was deemed not eligible for high dose interleukin-2 therapy. The patient enrolled in the AGS-003-006 study, to receive sunitinib in combination with individualized, autologous immunotherapy with AGS-003. The patient underwent partial left nephrectomy to reduce tumor burden, which also provided the tumor for AGS-003 manufacturing. She was then, per protocol, started on sunitinib

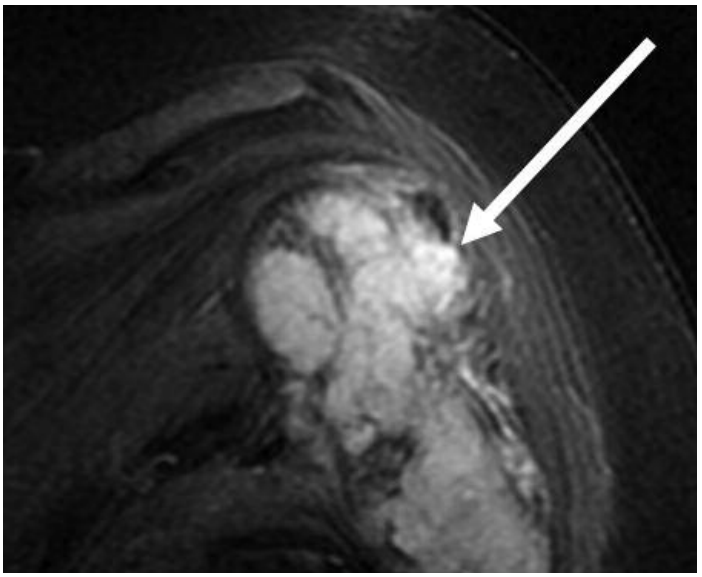

Figure 3A. Left humerus metastasis on MRI left upper extremity at presentation- Case 2

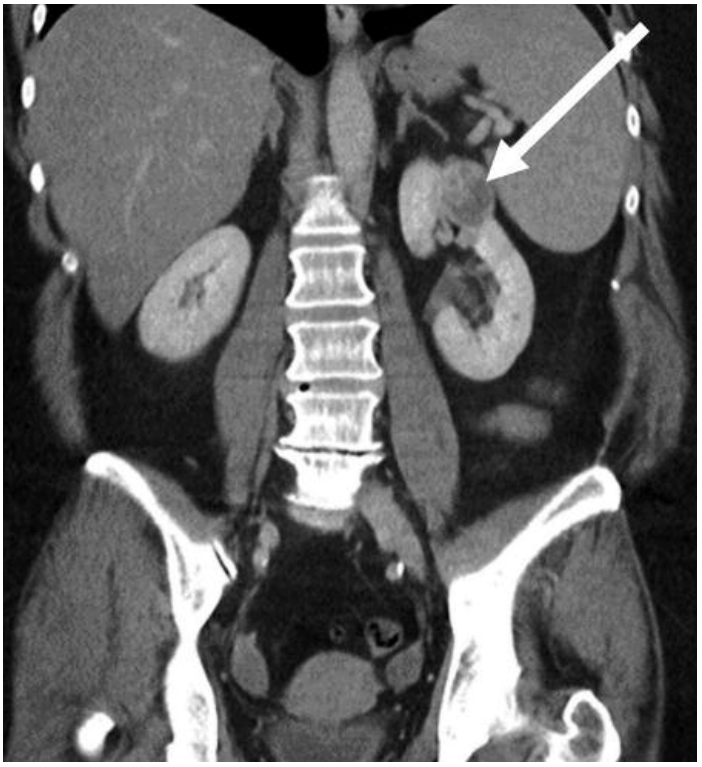

Figure 3B. Left renal lesion at start of therapy- Case 2

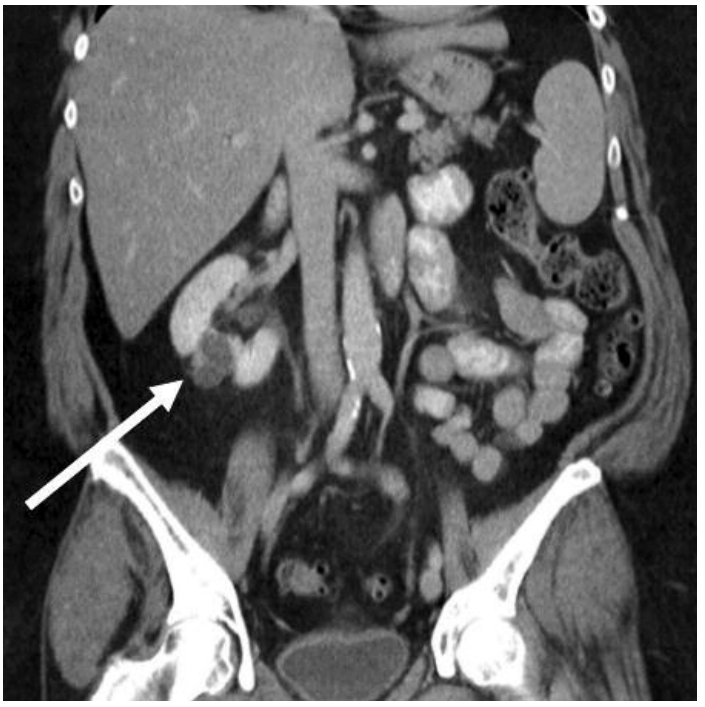

Figure 3C. Right Renal lesion at start of therapy- Case 2

post-surgery (50 mg orally once daily, 4 weeks on followed by 2 weeks off) and received AGS-003 (as described above). Post-nephrectomy, the patient's only measurable disease was limited to the right renal lesion.

After 3 months of therapy, the patient achieved a partial response in her right renal lesion, but had diarrhea, fatigue and depression with sunitinib therapy. Her symptoms were worse during the 4th week of therapy, and her sunitinib dosing was therefore changed to 50 mg daily, 3 weeks on and 3 weeks off. The patient continued to respond, but because of continued side effects including mucositis, fatigue and diarrhea, her sunitinib dose had to be further reduced to 25 mg once daily for 3 weeks on and 3 weeks off therapy. Remarkably at 7 years and 4 months from initiation of therapy, this patient continues on sunitinib and AGS-003 with no definite evidence of metastatic disease and a near complete radiographic response (**Figure 4A**, **Figure 4B**).

Unfortunately, samples were not available to complete the same type of immune function analysis on this patient as was done for Case 1.

Material and Methods

The two patients were enrolled in the study "Study Testing the Biologic Activity and Safety of an Immunotherapeutic in Patients With Newly Diagnosed Advanced Stage Kidney Cancer in Combination With a Marketed Renal Cell Carcinoma Treatment" NCT00678119 and with continued response were continued to be treated as part of a second study – "A Rollover Protocol for Subjects Previously Treated With AGS-003" - NCT01482949. The studies have been approved by the Interdisciplinary Site Specific Cancer Care team, Cancer Protocol Review Committee and Institutional Review Board at University of Minnesota.

AGS-003 production and the treatment paradigm of sunitinib in combination with AGS-003 were reported previously for the AGS-003-006 open label, single arm Phase 2 study.[9] Immune responses were assessed by multicolor flow cytometry using peripheral blood mononuclear cells (PBMCs) collected at Baseline prior to AGS-003 administration, and at the indicated time points post-dosing (**Figure 5A**). PBMCs were cultured *in vitro* with autol-

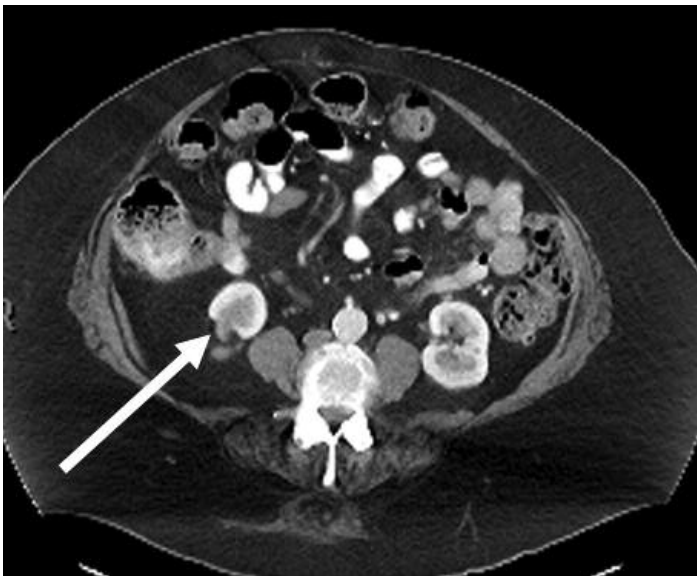

Figure 4A. Right Renal lesion after 6+ years of therapy- Case 2

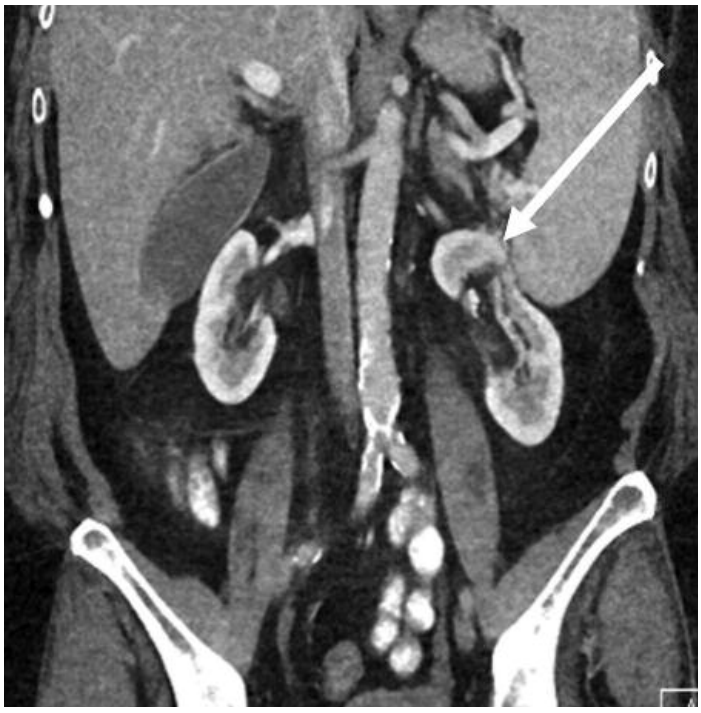

Figure 4B. Left Renal lesion after 6+ years of therapy- Case 2

ogous AGS-003 DCs as described previously,[9] and labeled with bromodeoxyuridine (BrdU) to track CTL proliferation after six days in culture. On Day 6, cultures were re-stimulated with autologous AGS-003 DC product, anti-CD107a antibody was added at the initiation of culture to allow detection of CTL degranulation during the 5 hour culture incubation period at 37°C. Cells were then stained for viability using Live/Dead Fixable Dye (Invitrogen) followed by surface staining with specific antibodies for the detection of viable CD3+ CD8+ T cells expressing CD28, CCR7, CD27 and CD45RA.

Cells were then fixed, permeabilized and DNase treated to detect BrdU (BD Biosciences). Intracellular staining for IFN-γ , Granzyme B (Grb), and Brdu was also performed. Cells were then transferred to BD TruCount Tubes for acquisition on a BD LSRII cytometer, with 400,000-600,000 events collected per sample. After *in vitro* stimulation, multicolor flow cytometry identified increases in the number of effector/memory CD3+/CD8+ T cell by their expression of surface markers CD28, CCR7, CD27 and CD45RA. CTL multi-functionality was determined by measuring the number of effector/memory CTL that proliferated, secreted IFN-γ or exhibited lytic activity (expression of Grb or CD107a). The number of CTL/ml within a given gate of interest was calculated using the following formula: (number of cellular events collected/number of Trucount beads collected) x (Trucount bead concentration)/collected volume) x 1000.

"This therapy offers durable responses to patients with non-favorable risk characteristics and remains promising. The ability to assess immunologic responses as intermediary biomarker for response will aid clinical development of this therapy which is often lacking for immunotherapies."

Immune Response Results

PBMCs collected at Baseline and during both the Induction Phase and first 36 months of AGS-003 dosing in the Booster Phase were available for Case 1 for the analysis of multi-functional CTL responses. As shown in **Figure 5A**, which plots the number of CD3+CD8+CD28+CD45RA- effector/memory CTLs for each functional marker tested at the indicated time points, increases in all immune markers were detected for this patient, with different time points where peak response was observed (cells/ml). Peak responses for proliferating (BrdU positive) CTLs were seen after 4 AGS-003 doses, reaching 3,572 cells/ml, and was sustained to 3,662 CTL/ml during Booster Phase dosing after 6 doses. CTLs with lytic activity (Grb positive) peaked during the Induction Phase after 4 doses at 6,756 cells/ml, and then subsequently decreased through the Booster Phase to numbers below Baseline. In addition, other notable increases in CTLs with effector function were detected for CTLs expressing INF-γ, which peaked during the Booster Phase after 10 AGS-003 doses, at 2,184 cells/ml. An increase in CTLs expressing the lytic marker CD107a, could also be detected at a lower number, ranging from 515 to 814 cells/ml, and peaked after 10 doses during the Booster Phase (**Figure 5A**).

Changes in CTLs expressing more than a single functional marker, defining multi-functionality, were also assessed by measuring the change in the number of proliferating CTLs with concurrent lytic activity as measured by the expression of Grb (**Figure 5B**). The frequency of BrdU/Grb double positive CD28+CD45RA- effector/memory CTLs peaked at 1.97% post the 5th AGS-003 dose compared to the Baseline frequency of 0.32%. As shown

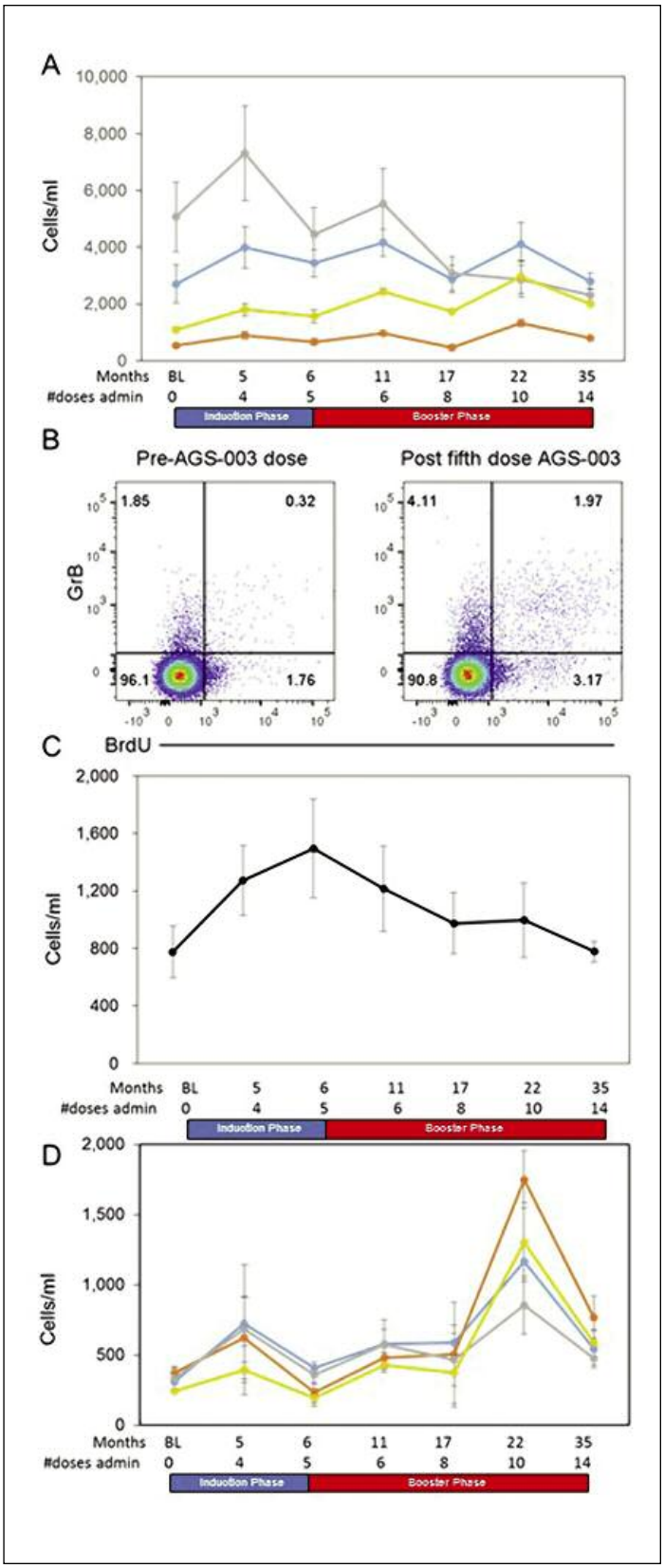

Figure 5. Analysis of multi-functional CTL response during AGS-003 administration. PBMCs collected at the indicated time points were stimulated in vitro with AGS-003 for 6 days. A) After stimulation effector function was detected by measuring the change in number of CTL-expressing functional markers. Cells/ml were calculated using Trucount tubes to measure the number of CTLs present in the viable CD3+/CD8+ T cell CD28+/CD45RA- phenotype gate that express each of the functional markers Brdu ■, CD107a ■, Grb ■, IFN-γ ■, by multi-color flow cytometry after 4 hours activation with AGS-003. B) Representative dot plots gated on the CD28+/CD45RA- CTL subset expressing GrB (y-axis) and BrdU (x-axis) prior to AGS-003 administration and after the 5th dose of AGS-003. C) Numbers of cells/ml in the double positive gate for Grb+/BrdU+ CD28+/CD45RA- CTL were plotted versus the indicated time points (months); D) Number of CTLs positive for all four markers CD28+/CCR7+/CD27+/CD45RA+ present in the viable CD3+/CD8+ T cell phenotype gate that express each of the functional markers Brdu ■, CD107a ■, Grb ■, IFN-γ ■, by multi-color flow cytometry after 4 hours activation with AGS-003. The number of doses administered at the indicated time points are shown along the x-axis with concurrent months calculated from Baseline (BL). Values are representative of triplicate samples shown with standard deviations. Statistical significance was determined using a 2-tailed student *t*-Test (*P*=<0.05).

in **Figure 5C**, which tracks the expansion of the number of BrdU/Grb double positive CTLs (cells/ml) over time, this response peaked at 6 months after the 5th dose of AGS-003, remained above Baseline into the Booster Phase after 10 doses AGS-003, and then returned to Baseline during the follow up period.

Given the remarkable resolution of metastatic lesions while on therapy, it was of interest to also examine the induced immune response present in this patient at the later time points throughout the Booster Phase. Interestingly during the Booster Phase of AGS-003 administration after 10 doses, increases in the numbers of CTLs with a more naïve like phenotype could be detected. These CTLs are positive for the expression of the combination of all four cell surface markers, CD28, CD27, CCR7 and CD45RA and proliferated after *in vitro* stimulation with AGS-003 product (**Figure 5D**).

Furthermore, these CTLs detected at the same time point are multi-functional by definition, secreting IFN- and containing lytic activity (both Grb and CD107 positivity). The ability to recall this population of CTLs after 10 doses of AGS-003 remained statistically significant over Baseline for all four functional markers. Statistically significant increases were still present for proliferating CTLs and CTLs expressing CD107a and IFN-γ out to the 35-month time point (after the 14th dose). Taken together, these data strongly support the important differentiation of an induced immune response during the Induction Phase of AGS-003 therapy from an effector/memory phenotype to a stable central memory phenotype that retains antigen specificity upon antigen recall.

Discussion

Treatment options for mRCC have improved dramatically over the last decade with the introduction of targeted therapies, but durable responses remain elusive, particularly in intermediate and poor risk patients.[3] New immunotherapy options have recently been approved or are in development that may offer further clinical benefit to these patients.[6-9]

AGS-003 is a novel, individualized, autologous DC-

based immunotherapy that uses autologous tumor RNA as the source of patient-specific tumor antigens to generate a product designed to induce a broad, adaptive immune response specifically directed to the patient's tumor antigens. Phase 2 (AGS-003-006) data from intermediate to poor risk mRCC patients treated with AGS-003 in combination with sunitinib (n=21) demonstrated increase in PFS and OS relative to published benchmark data,[10-12] with a third of patients (7/21) surviving more than 4.5 years; it was also shown to be well tolerated with toxicity being primarily related to the concomitant sunitnib therapy.[9]

Overall, 9/21 (43%) patients in this study had a partial response from Screening, median OS across risk groups was 30.2 mo (intermediate risk[1], 61.9 mo; poor risk1, 9.1 mo) and median PFS was 11.2 mo (intermediate risk1, 19.4 mo; poor risk1, 5.8 mo). Based on published data from a randomized study of sunitnib versus IFN-γ (n=750), median OS in patients meeting Memorial Sloan-Kettering Cancer Center (MSKCC) criteria for intermediate risk mRCC treated with sunitinib was 20.7 months (95% CI, 18.2 to 25.6 months), and was 5.3 months (95% CI, 4.2 to 10 months) for the poor risk group.[10] Using the Heng prognostic criteria, intermediate risk patients with mRCC (n=301) have been reported to have a median OS of 27 mo, and in the poor risk group, median OS was 8.8 months (n=152).[11]

A more recently published retrospective analysis of treatment outcomes based on data from the International mRCC Database Consortium (IMDC) included a larger proportion of patients who have received more contemporary targeted therapies.[12] In the subgroup of patients with intermediate or poor risk mRCC, paralleling those enrolled in the AGS-003-006 study, the median OS was 14.7 mo (n=1,189) and median PFS was 5.6 mo (n=1,174).

In this report we provide an update on two exceptional long-term responders from this Phase 2 study, who have had sustained durable clinical responses spanning over 7 years on combination immunotherapy. Moreover, unique, longitudinal immune response data available from one of these long-term responders, document the important induction of CD28+CD45RA- effector/memory CTLs after 5 doses of AGS-003; an increase in this population of CTLs from Baseline was shown to correlate with improved OS in AGS-003-006 in patients who completed the Induction Phase (≥ 5 doses).[9] Furthermore in this patient, expanded immune response analyses demonstrated the detection of multi-functional CTLs that have a more naïve-like phenotype based on the expression of all four phenotypic makers CD28, CCR7, CD27 and CD45RA, after subsequent AGS-003 dosing in the Booster Phase.

We hypothesize that these CTLs become functional when stimulated with DCs (AGS-003), but retain qualities of both naïve CTLs, i.e., they proliferate upon seeing antigen, and antigen-experienced CTLs, i.e., they also retain the rapid ability to produce cytokines and acquire lytic function. These naïve-like effector/memory CTLs may importantly represent a subset of CTLs with the ability to differentiate into immediate effector CTLs upon antigen re-encounter.[13,14] Taken together, these data now demonstrate that AGS-003-induced CTL responses are maintained in a multi-functional state, inducing proliferating CTLs with both concurrent cytolytic activity and the ability to secrete IFN-γ. The presence of these expanded effector/memory CTLs with cytolytic function, through the production of Granzyme B and secretion of IFN-γ may serve as an important surrogate marker of the immunological impact of AGS-003 treatment on tumor progression. Therefore, tracking effector/memory CTLs, concurrently with monitoring clinical outcomes, may prove to be a critical link between immunological responses and tumor responses in subjects with mRCC.

Conclusions

AGS-003 when administered along with sunitinib as frontline therapy is very well tolerated without any significant additional side effects over single agent sunitinib therapy and can be continuously administered for period of years without significant treatment burden to the patients. This therapy offers durable responses to patients with non-favorable risk characteristics and remains promising. The ability to assess immunologic responses as intermediary biomarker for response will aid clinical development of this therapy which is often lacking for immunotherapies.

Ethics, Consents and Permission

Patients were enrolled in phase II clinical trial NCT00678119 and later have continued on rollover protocols who continued to respond on therapy - NCT01482949. Patients were consented for both these studies by protocol which has been approved by local IRB. Subjects have consented to publish this case report as long term responders.

Disclosures/Conflict of Interest/ Competing Interests

Drs. Gautam Jha and Arkadiusz Dudek declare no competing interests or conflict of interest. Drs. Mark DeBenedette, Lee Allen and Shawn Leland are employees with Argos therapeutics and are shareholders in the company. Correlative studies including immune-monitoring was done by the team at Argos.

Acknowledgements

Interdisciplinary Site Specific Cancer Care team, Cancer Protocol Review Committee and Institutional Review Board at University of Minnesota for study review, approval and monitoring.

Authors Contributions

GJ wrote, reviewed and edited the manuscript before submission. AD contributed substantially to the discussion, review and editing of manuscript before submission. MD contributed to the writing and design of the manuscript,

designed and supervised the immune monitoring program. LFA was involved in the review and analysis of data, and the development, revision and finalization of the manuscript. SML was involved in the review and analysis of data, and the development, revisions and finalization of the manuscript.

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reported in the next issue of the *Kidney Cancer Journal*.

ESMO will also bring the heavily publicized results of S-TRAC which has been announced as a positive adjuvant study using sunitinib for patients who have had complete resection of high-risk tumors. This was a startling press release in light of negative findings of the ASSURE (E2805) study- a much larger study with a wider range of patients. Even with positive findings from S-TRAC, our approach to adjuvant therapy will require much discussion.

A second meeting next month, and the only international meeting to focus specifically on RCC, is the 15th International Kidney Cancer Symposium (IKCS), November 4-5 in Miami. The Kidney Cancer Association will make virtual presentations of the scientific sessions available on its website within several weeks of the conference. http://www.kidneycancer.org/knowledge/learn/medical-education-cme. This year's agenda will address many of the issues of combinations of therapy discussed by Nicholas J. Vogelzang, MD, in this issue. (See the KCJ Interview, page 98.) Although this conference presents substantial data from pivotal trials, the informal atmosphere during meeting breaks enables attendees to get together with presenters and review posters in a great exchange of information.

The 2017 Genitourinary Cancers Symposium, known to many as GU ASCO, will convene in Orlando, February 16-18. The agenda will include additional new trial data that will have a significant impact on the treatment algorithm for RCC.

All of these developments will impact our approach to RCC. The rapid succession of these reports underscores how quickly clinical decision-making has need to advance. While, this continued evolution is frustrating for those trying to analyze an ever evolving system, the more important and good news is that we have great options for patients and excellent resources and venues with which to evaluate these options.

Edwin M. Posadas, MD, FACP
Guest Editor

(continued from page 84)

Conclusion: PN is a viable treatment option for larger renal tumors, as it offers acceptable surgical morbidity, equivalent cancer control, and better preservation of renal function, with potential for better long-term survival. For T2 tumors, PN use should be more selective, and specific patient and tumor factors should be considered. Further investigation, ideally in a prospective randomized fashion, is warranted to better define the role of PN in this challenging clinical scenario. This study performed a cumulative analysis of the literature to determine the best treatment option in cases of localized kidney tumor of higher clinical stage (T1b and T2, as based on preoperative imaging). The findings suggest that removing only the tumor and saving the kidney might be an effective treatment modality in terms of cancer control, with the advantage of preserving the kidney function. However, a higher risk of perioperative complications should be taken into account when facing larger tumors (clinical stage T2) with kidney-sparing surgery.

European Association of Urology guidelines for clear cell renal cancers that are resistant to vascular endothelial growth factor receptor-targeted therapy. Powles T, Staehler M, Ljungberg B, et al. *Eur Urol*. 2016 Jun 24
The European Association of Urology renal cancer guidelines panel recommends nivolumab and cabozantinib over the previous standard of care in patients who have failed one or more lines of vascular endothelial growth factor-targeted therapy. New data have recently become available showing a survival benefit for cabozantinib.

Policy Issues in the Clinical Development and Use of Immunotherapy for Cancer Treatment: Proceedings of a Workshop. National Cancer Policy Forum; Board on Health Care Services; Health and Medicine Division; National Academies of Sciences, Engineering, and Medicine. Washington (DC): National Academies Press (US); 2016.
Summary: Immunotherapy is a form of cancer therapy that harnesses the body's immune system to destroy cancer cells. In recent years, immunotherapies have been developed for several cancers, including advanced melanoma, lung cancer, and kidney cancer. In some patients with metastatic cancers who have not responded well to other treatments, immunotherapy treatment has resulted in complete and durable responses. Given these promising findings, it is hoped that continued immunotherapy research and development will produce better cancer treatments that improve patient outcomes. With this promise, however, there is also recognition that the clinical and biological landscape for immunotherapies is novel and not yet well understood. For example, adverse events with immunotherapy treatment are quite different from those experienced with other types of cancer therapy. Similarly, immunotherapy dosing, therapeutic responses, and response time lines are also markedly different from other cancer therapies. To examine these challenges and explore strategies to overcome them, the National Academies of Sciences, Engineering, and Medicine held a workshop in February and March of 2016. This report summarizes the presentations and discussions from the workshop.

Immunomodulatory Activity of Nivolumab in Metastatic Renal Cell Carcinoma. Choueiri TK, Fishman M, Escudier B, et al. *Clin Cancer Res*. 2016 May 11.
Summary: Nivolumab was administered intravenously every 3 weeks at 0.3, 2.0, or 10 mg/kg to previously treated patients and 10 mg/kg to treatment-naïve patients with mRCC. Baseline and on-treatment biopsies and blood were obtained.. In 91 treated patients, median overall survival (95% CI) was 16.4 months (10.1-not reached [NR]) for nivolumab 0.3 mg/kg, NR for 2 mg/kg, 25.2 months (12.0-NR) for 10 mg/kg, and NR for treatment-naïve patients. Median percent change from baseline in tumor-associated lymphocytes was 69% (CD3+), 180% (CD4+), and 117% (CD8+). Of 56 baseline biopsies, 32% had {greater than or equal to}5% PD-L1 expression, and there was no consistent change from baseline to on-treatment biopsies. Transcriptional changes in tumors on treatment included up-regulation of interferon- -stimulated genes (e.g., CXCL9). Median increases in chemokine levels from baseline to C2D8 were 101% (CXCL9) and 37% (CXCL10) in peripheral blood. No new safety signals were identified.
Conclusion: Immunomodulatory effects of PD-1 inhibition were demonstrated through multiple lines of evidence across nivolumab doses. Biomarker changes from baseline reflect nivolumab pharmacodynamics in the tumor microenvironment. These data may inform decisions about potential combinations. KCJ

MEDICAL INTELLIGENCE

(continued from page 85)

Key Cabozantinib Clinical Data Presentation Given Priority at ESMO 2016 Congress

SOUTH SAN FRANCISCO— Exelixis, Inc. has provided an update on the timing of a key data presentation for cabozantinib at the European Society for Medical Oncology (ESMO) 2016 Congress, to be held October 7-11, in Copenhagen, Denmark. Detailed results from CABOSUN, the randomized phase 2 clinical trial of cabozantinib compared with sunitinib in patients with previously untreated advanced renal cell carcinoma (RCC), has been selected for the Presidential Symposium 3 session on October 10.

The late-breaking CABOSUN abstract was initially slated for an oral presentation at a Proffered Paper session on October 8.. Exelixis previously announced that data from the Exelixis-discovered compounds cabozantinib and cobimetinib would be the subject of fifteen presentations at the ESMO 2016 Congress.

15th International Kidney Cancer Symposium Offers Exciting Agenda

MIAMI—Bringing together key individuals and representatives from leading laboratories and centers working with renal cell carcinoma, the 15th International Kidney Cancer Symposium seeks to provide a forum for the exchange of ideas and information that will continue to frame directions for future research and treatment. The Symposium will be held November 4-5 at the Miami Marriott Biscayne Bay.

A wide ranging agenda covering emerging trends in diagnosis and treatment, analyses of new data from pivotal clinical trials, case reports, and abstracts and posters will provide attendees with the most comprehensive symposium devoted exclusively to kidney cancer topics.

To register for this CME meeting, visit the following website: http://www.outreach.niu.edu/outreach/conference/maps/2016kcamiamiregform.pdf. KCJ

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

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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.

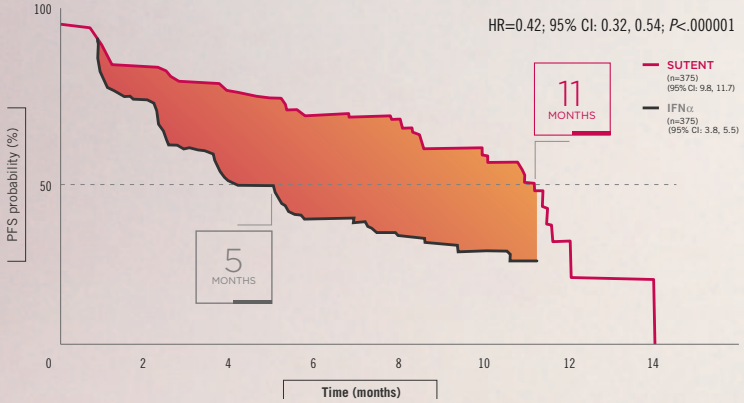
SUTENT® (sunitinib malate) IS INDICATED FOR THE TREATMENT OF ADVANCED RENAL CELL CARCINOMA (RCC).

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

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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

WEEK 1	WEEK 2	WEEK 3	WEEK 4	WEEK 5	WEEK 6
on	on	on	on	off	off

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

WEEK 1	WEEK 2	WEEK 3
on	on	off

- 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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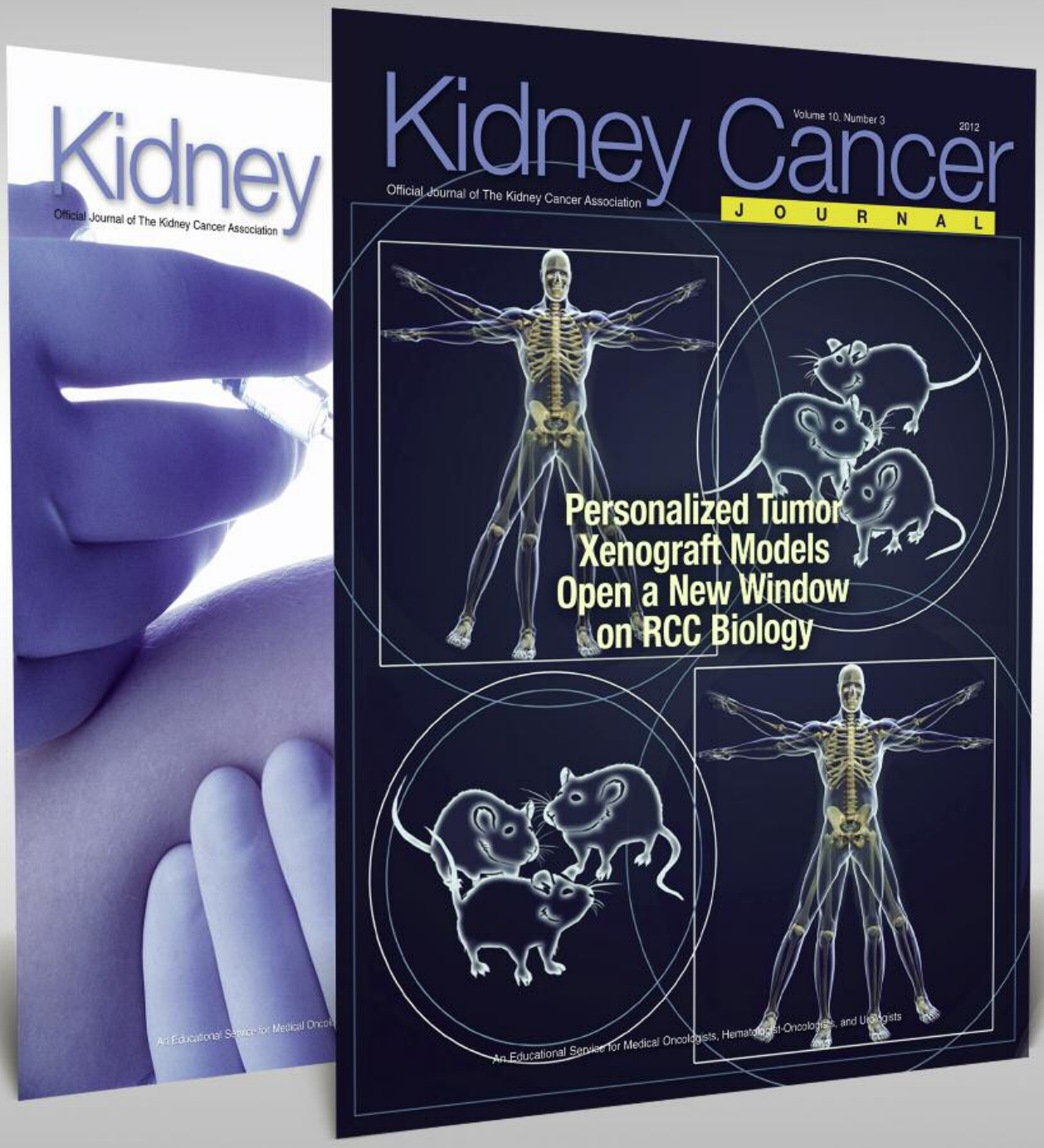

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