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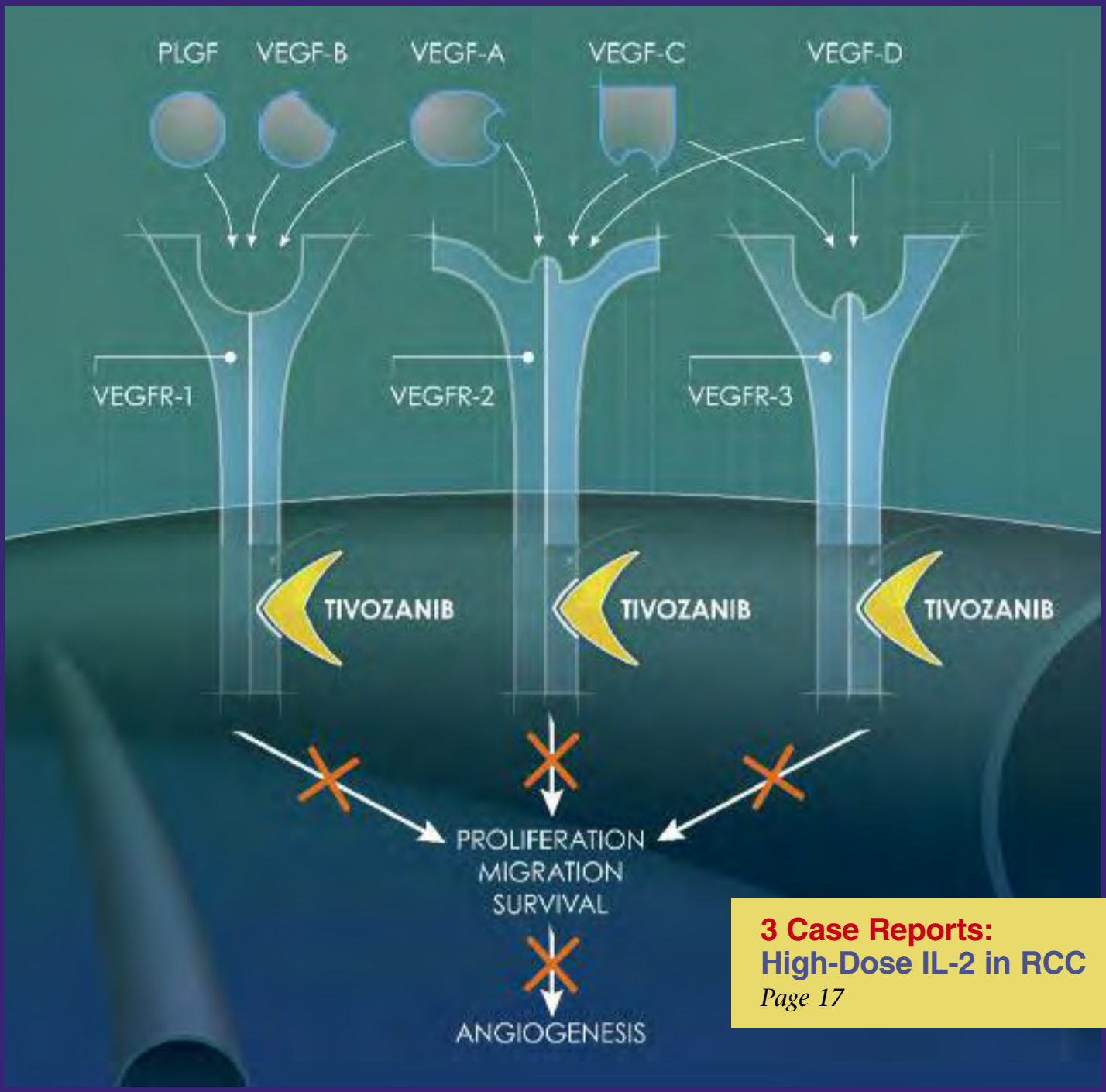
The Next Generation of Targeted Therapy: Optimizing VEGF Inhibition, Reducing Off-Target Toxicity



3 Case Reports:
High-Dose IL-2 in RCC
Page 17

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

SUTENT is indicated for the treatment of advanced renal cell carcinoma (RCC).

LEAD WITH EFFICACY. LEAD WITH SUTENT.

(SUNITINIB MALATE)

SUTENT: PROVEN EFFICACY IN 1ST-LINE mRCC VS IFNα*

MORE THAN DOUBLED MEDIAN PFS

- 11 months vs 5 months with IFNα (95% CI: 9.8, 11.7 and 3.8, 5.5, respectively; *P*<.000001)
- 58% reduced risk of progression or death (HR=0.42; 95% CI: 0.32, 0.54)

DEMONSTRATED 5-FOLD HIGHER ORR

- 39% vs 8% with IFNα (95% CI: 34.0, 44.3 and 5.7, 11.8, respectively; *P*<.000001) in the second analysis (June 2007)[1]
- 28% vs 5% with IFNα (95% CI: 23.0, 32.3 and 3.3, 8.1, respectively; *P*<.001) in the first analysis (November 2005)

ALSO ACHIEVED MORE THAN 2 YEARS' MEDIAN OS

- 26.4 months vs 21.8 months with IFNα (HR=0.82; 95% CI: 0.673, 1.001; *P*=.051)[1]

AN ESTABLISHED SAFETY PROFILE

- The most common adverse reactions (ARs) occurring in ≥20% of patients receiving SUTENT for treatment-naïve metastatic RCC (all grades, vs IFNα) were 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%)

*All data are from the large (N=750), phase 3, randomized, multicenter trial comparing SUTENT with IFNα in patients with treatment-naïve metastatic RCC.

ORR=objective response rate; OS=overall survival; PFS=progression-free survival.

Reference: 1. Data on file. Pfizer Inc, New York, NY.

Please see study description and brief summary, including boxed warning, on the following page.

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.

Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant.

Left ventricular ejection fraction declines to below the lower limit of normal have occurred. 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.

Hemorrhagic events including tumor-related hemorrhage, some of which were fatal, have occurred. Perform serial complete blood counts (CBCs) and physical examinations.

Thyroid dysfunction may occur. Monitor thyroid function in patients with signs and/or symptoms of hypothyroidism or hyperthyroidism and treat per standard medical practice.

Adrenal hemorrhage was observed in animal studies. Monitor adrenal function in case of stress such as surgery, trauma, or severe infection.

CBCs and serum chemistries should be performed at the beginning of each treatment cycle.

Dose adjustments are recommended when administered with CYP3A4 inhibitors or inducers.

The most common grade 3/4 ARs (occurring in ≥5% of SUTENT patients) were 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 receiving SUTENT (vs IFNα) included 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%).

capsules
SUTENT®
sunitinib malate
The Proven Path

Results of the phase 3, randomized, multicenter, international trial. 750 treatment-naïve patients were treated with either 50-mg SUTENT once daily in cycles of 4 weeks on/2 weeks off, or 9 MIU IFNα 3 times per week (administered subcutaneously) until disease progression or study withdrawal. Primary endpoint was progression-free survival, and secondary endpoints included objective response rate by Response Evaluation Criteria in Solid Tumors, overall survival, and safety.

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]*

INDICATIONS 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.

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/Pregnancy Category D. 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. 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 receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with SUTENT.

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).

Left Ventricular Dysfunction. 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, myocardial disorders and cardiomyopathy, some of which were fatal, have been reported through post-marketing experience. More patients treated with SUTENT experienced decline in left ventricular ejection fraction (LVEF) than patients receiving either placebo or 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.

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 patient (<1%) on IFN-α. SUTENT dosing was reduced or temporarily delayed for hypertension in 21/375 patients (6%) on the treatment-naive 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 in gastrointestinal stromal tumor (GIST) or RCC patients 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. Fatal pulmonary hemorrhage occurred in 2 patients receiving SUTENT on a clinical trial of patients with metastatic non-small cell lung cancer (NSCLC). Both patients had squamous cell histology. SUTENT is not approved for use in patients with NSCLC. 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.

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 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.

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 577 patients who participated in the double-blind treatment phase of a placebo-controlled trial (n=202) for the treatment of GIST or an active-controlled trial (n=375) for the treatment of RCC. The 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 or RCC 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-naive 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)
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)
Alopecia	51 (14)	0 (0)	34 (9)	0 (0)
Erythema	46 (12)	2 (<1)	5 (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 rare (<1%) reports 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. Cases of serious infection (with or without neutropenia), in some cases with fatal outcome, have been reported. Cases of myopathy and/or rhabdomyolysis with or without acute renal failure, in some cases with fatal outcome, have been reported. Patients with signs or symptoms of muscle toxicity should be managed as per standard medical practice. Thrombotic microangiopathy has been reported in patients on SUTENT. Suspension of SUTENT is recommended; following resolution, treatment may be resumed at the discretion of the treating physician. Cases of fatal hemorrhage associated with thrombocytopenia have been reported. Pulmonary embolism, in some cases with fatal outcome, has been reported. Cases of renal impairment and/or failure, in some cases with fatal outcome, have been reported. Cases of proteinuria and rare cases of nephrotic syndrome have been reported. 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. Hypersensitivity reactions, including angioedema, have been reported. Cases of fistula formation, sometimes associated with tumor necrosis and/or regression, in some cases with fatal outcome, have been reported.

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.

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.

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]*.

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 sunitinib or its primary active metabolite are excreted in human milk. Because drugs are commonly excreted in human milk and because of the potential for serious adverse reactions in nursing infants, 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 *[see Nonclinical Toxicology]*.

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 MRCC 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 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.

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. A few 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

Although definitive carcinogenicity studies with sunitinib have not been completed, carcinoma and hyperplasia of the Brunner's gland of the duodenum have been observed at the highest dose tested in H2ras transgenic mice administered doses of 0, 10, 25, 75, or 200 mg/kg/day for 28 days. 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 (approximately 5.1 times the AUC in patients administered the RDD), while uterine changes (endometrial atrophy) were noted at ≥2 mg/kg/day (approximately 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 approximately 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 approximately 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 approximately 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 in patients 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.

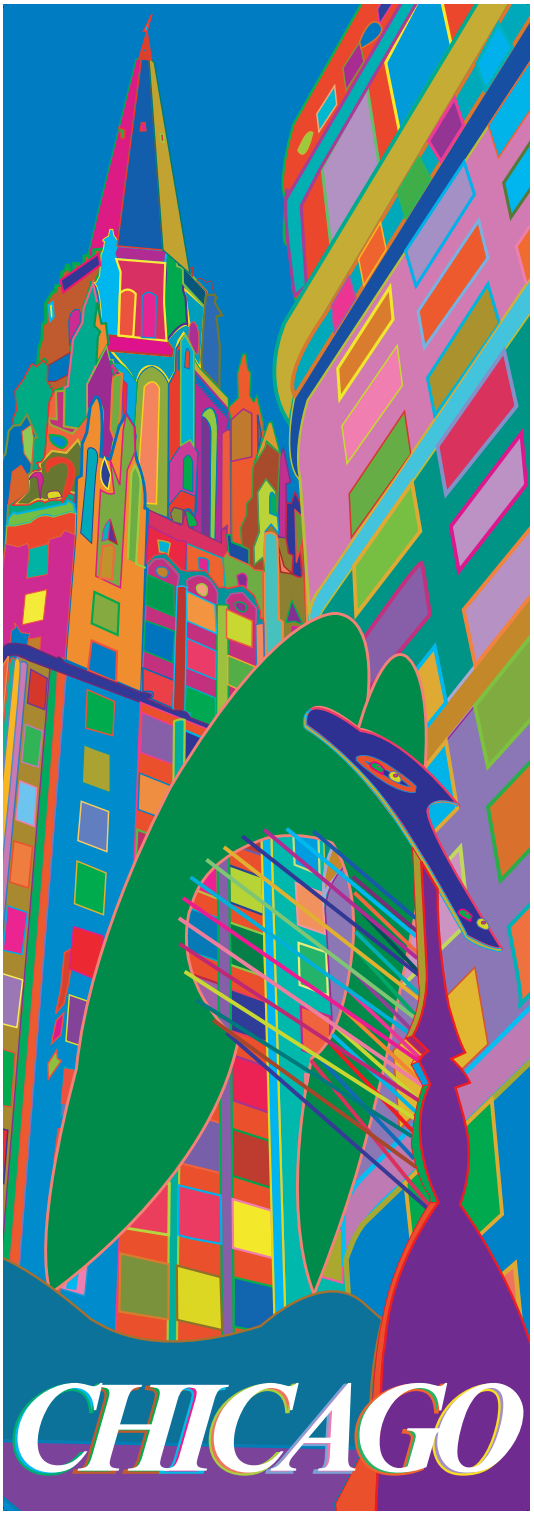
Other Common Events. Other commonly reported adverse events included fatigue, high blood pressure, bleeding, swelling, mouth pain/irritation and taste disturbance.

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]*.

Rx only

Revised: July 2010

Save the Date!



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About the Cover
Illustration depicts inhibition of three vascular endothelial growth factor (VEGF) receptors critical in the pathogenesis of renal cell carcinoma (RCC), thereby preventing disease progression. New targeted therapies such as tivozanib, now in phase 3 clinical trials, are considered more effective for RCC because of their improved selectivity for and inhibition of all three VEGF receptors. Safety profiles are also reportedly improved. (Illustration courtesy of AVEO Pharmaceuticals. Copyright 2011)

KCJ TABLE OF CONTENTS

KCJ GUEST EDITOR'S MEMO

"Moving the Needle" a Bit Further Toward a Paradigm Shift in Therapy


Bradley C. Leibovich, MD

For the 30,000 attendees who traditionally attend the annual scientific sessions of the American Society of Clinical Oncology (ASCO), this event represents a time when oncologists, urologists, and other professionals involved with kidney cancer management are most likely to see dramatic shifts in the treatment paradigm and new perspectives to emerge on a multitude of issues. Although we have not seen such a dramatic shift in the treatment algorithm for several years—and may not see it for at least another year—there are promising signs that we are on the verge of a new era in targeted therapies. Presentations at this year's meeting will no doubt build excitement and hopefully "move the needle" a bit closer toward that goal. New data are emerging from ongoing phase 3 clinical trials that suggest what we can expect in the years ahead.

The ensuing article in this issue of the *Kidney Cancer Journal* by Robert J. Motzer, MD, provides valuable insights into this new era as antiangiogenic agents such as tivozanib and axitinib undergo evaluation in trials keenly watched for their potential impact on the treatment algorithm. Dramatic changes in the treatment algorithm are on the horizon and Dr Motzer chronicles progress made in trials to date and efforts to validate the use of "cleaner" targeted therapies that provide enhanced efficacy and an improved safety profile. For now, however, another "banner year" for treatment, as Michael Atkins, MD, announced at an earlier ASCO meeting, is not here yet. Today, we need to take note of how an improved understanding of the molecular underpinnings of renal cell carcinoma (RCC) raise expectations for therapeutic approaches and how progress is coming along toward more effective vascular endothelial growth factor (VEGF) inhibition.

Currently, the gap between molecular findings and clinical outcomes remains large, as was noted last year in a report by a task force established by the National Comprehensive Cancer Network on optimizing targeted therapies. An improved understanding of the molecular factors involved in the development and progression of RCC will help reduce this gap. Correlation of molecular changes with patient outcomes will be an essential component of this research, and we look toward the progress seen in clinical trials reported at this year's ASCO meeting.

It is my pleasure to serve as the Guest Editor of the *Kidney Cancer Journal*; and I look forward to the subsequent issue that will feature a full report on new data presented on RCC at the 2011 ASCO sessions.

This issue also provides dynamic content on a broad spectrum of other topics essential to an improved understanding of the disease and its management. On behalf of the journal and its Medical Advisory Board, I extend my appreciation to my esteemed colleagues for their valuable contributions and perspectives on current thinking in kidney cancer management as we strive toward a new era in the quality of patient care.

Bradley C. Leibovich, MD
Guest Editor

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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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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Tracking Trends From Web-based Sources, Translational Research, the FDA, and Patient Registries

New data on sunitinib clarifies dosing schedule

ORLANDO, FL—Data presented at the 2011 ASCO GU Cancer Symposium from the phase 2 Renal EFFECT trial adds to the established clinical experience and supports the dosing profile of sunitinib (Sutent®). The safety profile observed in patients treated with a regimen of 37.5 mg continuous daily dosing compared with the approved treatment cycle of 50 mg daily, given on a 4 weeks on, 2 weeks off treatment schedule, were similar. Efficacy endpoints, such as overall response rate and overall survival (OS) showed similar results between the 2 doses, while a trend toward inferior time to disease progression was noted with the continuous dosing regimen. In addition, data from a retrospective, exploratory analysis of 5 sunitinib clinical trials in advanced renal cell carcinoma (RCC) suggest that development of treatment-induced hand-foot syndrome (HFS) may serve as a predictive biomarker of efficacy. According to findings from this analysis, patients with advanced RCC who developed sunitinib-associated HFS had a significantly better clinical outcome than those who did not develop HFS, with respect to all efficacy endpoints analyzed, including progression-free survival (PFS) and OS. Overall, patients who did not develop HFS still had substantial benefit from sunitinib, although the presence of HFS identified a subset of patients who had better efficacy on treatment. While additional prospective studies are needed to validate these findings, these data contribute to a growing body of knowledge regarding the adverse effect profile for Sutent and potential correlations with efficacy.

Marketing rights for new adjuvant agent granted to Prometheus Laboratories

MUNICH—WILEX AG has announced the granting of US commercialization rights for RENCAREX® (girentuximab) to Prometheus Laboratories Inc, San Diego. Prometheus is an established specialty pharmaceutical and diagnostics company with a proven track record in gastroenterology and oncology. Prometheus will co-fund a portion of the ongoing development of RENCAREX, which is a phase 3 product candidate for adjuvant use in non-metastatic clear cell renal cell cancer. The deal includes the potential development in further indications. Prometheus markets Proleukin®, an oncology product indicated for metastatic renal cell carcinoma and metastatic melanoma, in the United States. If RENCAREX receives FDA approval, Prometheus would be able to offer a treatment for both adjuvant and metastatic kidney cancer.

Renal cancer drug temsirolimus shows promise against mesothelioma

DENVER, CO—Temsirolimus may increase the effectiveness of chemotherapy for mesothelioma, according to a study published in the May issue of the *Journal of Thoracic Oncology*. Temsirolimus, a kinase inhibitor, blocks the action of mammalian target of rapamycin (mTOR), a protein that regulates cell growth, which can slow tumor growth. It is used to treat advanced renal cell carcinoma. But researchers in Austria have found that temsirolimus may also slow the growth of malignant pleural mesothelioma cells. Mesothelioma, a cancer that is usually caused by exposure to asbestos and may not appear until 30 to 50 years after exposure, frequently resists chemotherapy and radiation treatment.

The researchers found that temsirolimus strongly blocked mTOR-mediated signals and had a cytostatic, or growth-stopping, effect on all mesothelioma cells. However, mesothelioma cells that were resistant to cisplatin, a widely used chemotherapy drug, showed hypersensitivity against temsirolimus. This suggests that mTOR inhibitors such as temsirolimus might provide a promising treatment strategy either in combination with chemotherapy or as second-line treatment after chemotherapy failure.

Kidney cancer on the rise: improved detection, obesity epidemic may play role

ORLANDO, FL—The number of people with kidney cancer in the United States has risen steadily since 1975 and, since 1991, the greatest increase has been among younger people. From 1975 to 1990, the number of new cases increased on average by 3.6% annually, says study leader Kenneth G. Nepple, MD, a fellow in urologic oncology at Washington University in St. Louis. From 1991 to 2006, cases rose on average by 2.9% per year. Nepple told WebMD that cases increased in all age groups from 1975 to 2006. But the proportion of patients diagnosed when they were younger than age 65 increased from 45.9% in 1991 to 55.3% in 2006, according to information presented at the 2011 GU Cancers Symposium. Some of the rise comes from increased detection on CT scans, says Christopher G. Wood, MD, Professor of Urology at the University of Texas M.D. Anderson Cancer Center in Houston. The researchers used data from the National Cancer Institute's Surveillance, Epidemiology, and End Results cancer registry database to look at renal cancer trends from 1975 to 2006. The database covers about one-fourth of the US population.

Hepatitis C tied to higher kidney cancer risk

DETROIT—New research suggests that the hepatitis C virus is linked to a much higher risk of developing kidney cancer. A study of more than 67,000 patients enrolled in the Henry Ford Health System from 1997 through 2008 found that 0.6% of patients with hepatitis C developed kidney cancer, double the rate of other patients, and the increased risk

(continued on page 41)

Essential Peer-Reviewed Reading in Kidney Cancer

The peer-reviewed articles in this section were selected by the Guest Editor, Bradley C. Leibovich, MD, for their timeliness, importance, and relevance to clinical practice or translational research.

Sunitinib in Metastatic Renal Cell Carcinoma: Recommendations for Management of Noncardiovascular Toxicities

Kollmannsberger C, Bjarnason G, Patrick Burnett P, et al. *Oncologist*. 2011; pre-print abstract. (Editor's note: Will be published in May issue; Vol. 16, Number 5).

Summary: The multitargeted tyrosine-kinase inhibitor sunitinib has emerged as one of the standards of care for good- and intermediate-risk metastatic renal cell carcinoma. Although generally associated with acceptable toxicity, sunitinib exhibits a novel and distinct toxicity profile that requires monitoring and management. Fatigue, diarrhea, anorexia, oral changes, hand-foot syndrome and other skin toxicity, thyroid dysfunction, myelotoxicity, and hypertension seem to be the most common and clinically relevant toxicities of sunitinib. Drug dosing and treatment duration are correlated with response to treatment and survival. Treatment recommendations for hypertension have been published but, currently, no standard guidelines exist for the management of noncardiovascular side effects. To discuss the optimal management of noncardiovascular side effects, an international, interdisciplinary panel of experts gathered in November 2009. Existing literature on incidence, severity, and underlying mechanisms of side effects as well as on potential treatment options were carefully reviewed and discussed. On the basis of these proceedings and the thorough review of the existing literature, recommendations were made for the monitoring, prevention, and treatment of the most common noncardiovascular side effects and are summarized in this review. The proactive assessment and consistent and timely management of sunitinib-related side effects are critical to ensure optimal treatment benefit by allowing appropriate drug dosing and prolonged treatment periods.

Sunitinib in metastatic renal cell carcinoma patients with brain metastases.

Gore ME, Hariharan S, Porta C, et al. *Cancer*. 2011;117:501-509.

Summary: In a broad patient population with metastatic renal cell carcinoma (RCC), enrolled in an open-label, expanded access program (EAP), the safety profile of sunitinib was manageable, and efficacy results were encouraging. Previously treated and treatment-naive metastatic RCC patients ≥18 years received sunitinib 50 mg orally, once daily, on Schedule 4/2. Safety was assessed regularly, tumor measurements done per local practice, and survival data collected where possible.; 4371 patients were included in the modified ITT population, of whom 321 (7%) had baseline brain metastases and had received a median of 3 treatment cycles (range 1-25). Reasons for their discontinuation included lack of efficacy (32%) and adverse events (8%). The most common grade 3-4 treatment-related adverse events were fatigue and asthenia (both 7%), thrombocytopenia (6%), and neutropenia (5%), the incidence of which were comparable to that for the overall EAP population. Of 213 evaluable patients, 26 (12%) had an objective response. Median progression-free survival and overall survival were 5.6 months (95% CI, 5.2-6.1) and 9.2 months (95% CI, 7.8-10.9), respectively.
Conclusion: In patients with brain metastases from RCC, the safety profile of sunitinib was comparable to that in the general metastatic RCC population, and sunitinib showed evidence of antitumor activity.

Treatment of patients with small renal masses: a survey of the American Urological Association.

Breau RH, Crispen PL, Jenkins SM, et al. Blute ML. Journal of *Urology*. 2011;185:407-13, 2011.

Summary: In June 2009 American Urological Association members were solicited to complete an online survey. Respondents were asked their preferred treatment for 8 cases and 3 index patients. In each case computerized tomographic axial and schematic coronal images were provided. A total of 759 active urologists with varied training backgrounds and clinical practice settings completed the survey. Tumor size (OR 8.4, 95% CI 7.1-10.1), tumor depth (OR 19.2, 95% CI 14.8-25.0) and tumor location (OR 24.0, 95% CI 18.1-31.8) were markedly associated with preference for radical nephrectomy instead of partial nephrectomy. Fellowship trained urologists (OR 0.4, 95% CI 0.2-0.6) and urologists at academic hospitals (OR 0.6, 95% CI 0.4-0.9) were less likely to choose radical nephrectomy. Respondents were more likely to choose active surveillance in an older patient (OR 2.7, 95% CI 2.1-3.6) or in a patient with comorbidities (OR 10.0, 95% CI 8.0-12.4). Urologists were less likely to choose active surveillance for a 4 vs 2 cm tumor (OR 0.18, 95% CI 0.15-0.21). Active surveillance was chosen more often if the tumor was perihilar vs mid kidney (OR 2.0, 95% CI 1.8-2.3) or polar (OR 2.1, 95% CI 1.9-2.5).
Conclusion: There is considerable heterogeneity in the treatment of patients with clinical T1a tumors. Several factors explain these differences as selected treatments are independently associated with tumor, patient and urologist factors.

Hypothyroidism in patients with renal cell carcinoma: blessing or curse?

Schmidinger M, Vogl UM, Bojic M, et al. *Cancer*. 2011;117:534-44.

Summary: Sunitinib and sorafenib are tyrosine kinase inhibitors that have important antitumor activity in metastatic renal cell carcinoma (mRCC). Hypothyroidism constitutes a commonly reported side effect of both drugs, and particularly of sunitinib. The objective of this analysis was to investigate whether the occurrence of hypothyroidism during treatment with sunitinib and sorafenib affects the outcome of patients with mRCC. Eighty-seven consecutive patients with mRCC who were to receive treatment with sunitinib or sorafenib were included in a

(continued on page 42)

The Next Generation of Targeted Therapy: Optimizing VEGF Inhibition, Reducing Off-Target Toxicity

Robert J. Motzer, MD
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Despite advances in renal cell carcinoma therapy, significant unmet need persists. Currently available therapies provide less than one year of survival without disease progression and are associated with significant toxicities. One of the challenges remains the complexity of the vascular endothelial growth factor pathway; each of its many components play distinct roles in angiogenesis essential to the growth and survival of solid tumors. This review elucidates important information on an evolution in targeted therapy as we move beyond the first generation of tyrosine kinase inhibition and look toward a new era of more selective agents, prolonged progression free survival, and an improved safety profile. Now in ongoing or close to phase 3 trials, these new therapies could have an impact on the treatment algorithm for kidney cancer.

The next generation of targeted therapies for renal cell carcinoma (RCC) is on the horizon as clinical trials bring new and exciting treatment options further along the pipeline. Efforts to enhance therapeutic strategies continue to focus on optimally blocking the vascular endothelial growth factor (VEGF) pathway by inhibiting all three VEGF receptors. If this can be achieved, significant changes in the treatment algorithm could occur within the next few years or possibly sooner.

Despite advances in RCC therapies, a number of hurdles still stand in the way. Currently available therapies on average provide patients less than one year oryear or less of survival without disease progression and are associated with chronic significant toxicities that impact on quality of life.[1] There remains a need to developThis unmet need and the change newer agents with improved efficacy and reduced toxicity, and to set new standards for future treatment.represent are expected to drive management options in the near future. The need to develop and establish for new targeted therapies remainsis a priority. This translates from discovery almost perhaps as strong as it was 5 years ago when the first targeted agents dramatically revised the treatment algorithm and set a new direction in first-line kidney cancer management. We have observed a striking change in the treatment paradigm, breaking from the traditional approach of immunotherapy that had been the standard for the past two more than a decades. But unlike the earlier need when the shortcomings of biologic therapy were all too evident, including the low response rates and unacceptable toxicity associated with high-dose interleukin-2, the need now arises from the clinical experience gathered from first approved the first generation of targeted therapies, sunitinib and sorafenib largely based on data involving the sunitinib, sorafenib, and pazopanib. Despite the approval of these twohree tyrosine kinase inhibitors—among the 6 targeted therapies approved over the last 5 years—durable complete responses are still rare, the need for more selective agents capable of optimally targeting all 3 VEGF receptors is foremost, and the importance of avoiding off-target toxicities remains a major consideration. This review will focus on the experience to date of several approved anti-VEGF agents, the investigational work on the next generation of targeted therapies, and the implications for the treatment of RCC.

Several important differentiating features of RCC tumors, particularly those with predominantly clear cell or (conventional type) histology, enable us to understand the basis of anti-VEGF therapy:

- First is the clinical observation that RCC tumors routinely invade and grow within vascular spaces;
- Second, primary tumors typically, but not always, grow much larger than metastatic sites and that debulking these primary tumors improves long term survival;[2,3]
- Third, these tumors are relatively hypervascular and are commonly associated with both spontaneous central necrosis and bleeding risks;
- Most critically, that genetic alterations in the von Hippel Lindau (VHL) tumor suppressor gene are seen in the vast majority of clear cell RCC tumors.[3]

Keywords: targeted therapy; tivozanib; axitinib; dovitinib; vascular endothelial growth factor; tyrosine kinase inhibitor; renal cell carcinoma.

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These observations support the hypothesis that RCC tumors are unusually dependent upon their tumor microenvironment and in particular, on pro-angiogenic growth factors, most notably VEGF, to expand and progress. With the increased understanding of the molecular and genetic aspects of angiogenesis associated with metastatic RCC, ongoing investigations have focused on agents capable of avoiding the resistance frequently encountered with the first generation of targeted therapies. With multiple VEGF pathway-directed agents available, it becomes important to identify the targeting mechanisms, define safety and efficacy profiles and the extent of clinical cross-resistance. Still another important issue new trials address is the appropriate sequencing of agents, and much remains to be elucidated about this aspect of management, particularly as more targeted agents blocking different pathways become available. The rationale for the use of agents that block the VEGF pathway has been well described. Frequent and early loss of heterozygosity in the von Hippel-Lindau (*VHL*) gene allele has been demonstrated in 84% to 98% of sporadic clear-cell RCC, mutations in the remaining *VHL* allele have been detected in 34% to 57% of clear-cell cancers, and transcriptional inactivation of the gene by hypermethylation has been demonstrated in an additional 5% to 19% of these tumors.[4] In the absence of VHL protein, HIF-α accumulates and binds with HIF-β to form a transcriptional factor complex that induces transcription of various hypoxia-inducible genes, including vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). Overexpression of VEGF and PDGF, and their receptors, has provided rational targets for therapeutic intervention in RCC.

The Unmet Need: Challenges for the Next Generation of Targeted Therapy

Success and impact for VEGF-targeted therapies has been best measured by assessment of If progression-free survival. Demonstration of improvement in overall survival as an endpoint for phase 3 trials has been elusive with reported studies of VEGF-targeted agents were the only criterion to measure success, then existing VEGF-targeted therapies would show a robust and consistent result. Yet the data are far less convincing for overall survival. Despite a consistent pattern of PFS benefit demonstrated for VEGF-targeted therapies in patients with RCC, an overall survival advantage has not been clearly seen. All four of the first-line VEGF-targeted Phase III studies reported to date have demonstrated a trend towards an improvement in overall survival, but none have reached statistical significance. In large part this is thought to be due to subsequent treatment with other available VEGF targeted therapy.[5-8] The degree of improvement in overall survival by new targeted agents such as sunitinib or bevacizumab (plus interferon) is confounded by patients receiving targetedreceiving targeted therapies subsequently administered in second and third line to patients progressing on cytokine or placebo treatment on the control arm of pivotal phase 3 trials. Generally, the median survival of broadly defined patients with mRCC treated with interferon has ranged from 12 to 16 months; however, in the current studies median survival for the interferon control arms have ranged from 17.4 to 21.8 months.[7,8] Nevertheless, some secondary analyses suggest that patients who receive multiple VEGF-targeted therapies may in fact derive a much greater improvement in survival. For instance, in the AVOREN trial, patients treated with sunitinib subsequent to bevacizumab and interferon alpha had a median survival of 43.6 months, and 31.6 months for any second-line treatment in the CALGB 90206 study.[5]

Despite observed progress, tThe need to improve overall survival beyond that observed with with available VEGF-targeted therapies remains a critical objective and y is one of the unmet needs and a challenge for trials seeking to validate the efficacy of the next generation of targeted therapies. Current research has suggested that athe mechanism of resistance to VEGF targeted therapy is at least in part "angiogenic escape."[9] Angiogenic escape appears to be mediated by increases in a variety of proangiogenic and potentially decreases in angiostatic factors,[10-13] some of which have the potential for being targeted therapeutically. Understan-ding these mechanisms of resistance will inform efforts to extend the benefit of current treatment approaches. Solving the riddle of angiogenic escape is one of the greater challenges, but there are signs that some progress is being made, at least in clarifying the mechanisms.

Studies in mouse xenograft models using arterial spin labeling (ASL) MRI to study perfusion patterns following treatment with sunitinib and sorafenib have provided hypotheses on patterns of acquired resistance. The SPORE program, for example, has postulated intriguing hypotheses regarding the underlying mechanisms of resistance that could yield insights into clinical trial approaches for preventing or delaying angiogenic escape. The effort began with the development of mouse models of resistance and the implantation of human RCC cell lines into mice. Investigators then treated the tumors with either sunitinib or sorafenib and monitored their size until the tumors began regrowing. At different time periods before and during therapy, they imaged the tumors using arterial spin labeling (ASL) MRI, a technique for measuring perfusion (the degree of vascularization). According to the SPORE team, areas of reperfusion represent zones of growing tumor that are detected even while other areas of tumor are shrinking [from treatment]. ASL-MRI enables one to determine the true impact of therapy and identify the onset and mechanism of resistance. It also provides an opportunity to biopsy specific areas of the tumor that are exhibiting resistance, according to SPORE information.

Three key findings emerged from the xenograft models: (1) perfusion occurs before the tumor starts growing again – and may act as an early marker of tumor pro-

gression; (2) the appearance of perfusion on ASL-MRI mimics its histologic pattern; and (3) the more perfusion at baseline, the more likely the tumor is to respond to VEGF inhibitors. When the tumor's primary mechanism of survival is blocked it appears to switch to alternate mechanisms to reestablish perfusion. The exact mechanism of resistance to available targeted therapies in RCC remains largely unknown. Nevertheless, mounting evidence from RCC xenograft models suggests that even with continued VEGF suppression, there is restoration of vasculature visible at histopathologic examination and radiographic tumor perfusion studies.[13] This observation can translate into many therapeutic approaches, such as combinatorial approaches of different VEGF-targeted agents, in an effort to further suppress the VEGF pathway. However, this approach has resulted in significant toxicity with multitargeted agents such as sunitinib and sorafenib in combination with other agents. The combinations of bevacizumab with sorafenib or sunitinib are two examples where despite a high tumor response rates, the combinations were poorly tolerated and required dose reductions or discontinuation in a significant number of patients.[14,15]

Mechanisms of resistance

In some malignancies, such as lung cancer or CML, the development of resistance to a targeted therapy (e.g. erlotinib, imatinib) is often due to a mutation in a gene encoding a key receptor tyrosine kinase targeted by the drug. [16,17] VEGFR antagonism, however, likely capitalizes on the unique vulnerability of tumor endothelial cells, leaving damage to the tumor as a secondary effect. Thus, the mechanisms underlying the acquired resistance to VEGFR targeted therapy likely involve an adaptive response to increasing tumor hypoxia resulting from treatment-induced pruning of the tumor microcirculation rather than a stable genetic mutation in a tumor cell. In support of this possibility, acquired resistance to sorafenib or sunitinib therapy is accompanied by a restoration of tumor perfusion as assessed by Arterial Spin Labeled perfusion MRI (ASL MRI).[18] Moreover, tumors maintain their ability to respond to sorafenib upon tumor excision and reimplantation into a naive host and these perfusion changes also reverse in the setting of re-exposure to treatment.[13] Thus, resistance to VEGFR inhibition is likely due in part to up-regulation of angiogenic factors, the loss of angiostatic pathways or the adaptation of a tumor to survive hypoxic conditions.

The Need to Avoid Off-Target Toxicities

Off-target toxicity contributes to dose reduction and-often leads to a discontinuation of anti-VEGF therapy. Adverse events have been well documented and affect several important organ systems including gastrointestinal, cardiovascular, dermatologic, hematologic, renal, respiratory, musculoskeletal and various other and psychiatric, as well as constitutional symptoms. The route and class of VEGF-targeted therapy seem to make a difference. For orally administered multi-targeted TKIs the most common toxicities include gastrointestinal (diarrhea, nausea, vomiting, mucositis and dyspepsia) dermatologic (including hand foot syndrome, rash), fatigue/asthenia, hypertension, minor bleeding, elevated creatinine, liver function test abnormalities, as well as decreases in white blood cells, platelets and anemia. [19,20] Less common but more concerning for this class of therapy are the serious adverse events that have been seen, including potentially life threatening toxicities. Although the incidence is low, spontaneous, tumor-related and wound-related (dehiscence) bowel perforations, myocardial infarctions (MI), cerebrovascular accidents (CVA), reversible leukoencephalopathy syndrome (RPLS) and life-threatening infections have all been associated with VEGF-targeted therapies.

First Generation VEGF Inhibitors: Sunitinib, Sorafenib, Pazopanib

Sunitinib

Targeting Profile and Efficacy. Sunitinib (Sutent®) is an orally administered multitargeted tyrosine kinase inhibitor of vascular endothelial and platelet-derived growth factor receptors. A high response rate observed in the second-line treatment setting led to the design and conduct of a randomized phase III trial of sunitinib compared with interferon alfa (IFN-α) as first-line treatment of metastatic RCC.[7] The results of a preplanned interim analysis from the phase III trial showed superiority of sunitinib over IFN-α in progression-free survival time (11 *v* 5 months, respectively) by independent, third-party radiologic assessment ($P < .001$).

Sunitinib inhibits a number of growth factor receptors regulating both tumor cell proliferation/survival and tumor angiogenesis, including vascular endothelial growth factor receptors (VEGFRs)1–3, platelet-derived growth factor receptors (PDGFRs) α and β, c-Kit, FLT3, CSF1R, and RET. Median overall survival was greater in the sunitinib group than in the IFN-α group (26.4 *v* 21.8 months, respectively. By stratified log-rank test, the HR was 0.818 (95% CI, 0.669 to 0.999; $P = .049$). Within the IFN-α group, 33% of patients received sunitinib, and 32% received other vascular endothelial growth factor–signaling inhibitors after discontinuation from the trial. Median progression-free survival was 11 months for sunitinib compared with 5 months for IFN-α ($P < .001$). The objective response rate was 47% for sunitinib compared with 12% for IFN-α ($P < .001$). The most commonly reported sunitinib-related grade 3 adverse events included hypertension (12%), fatigue (11%), diarrhea (9%), and hand-foot syndrome (9%).

Side effect profile. The overall adverse event profiles for sunitinib and IFN-α are consistent with those reported previously in the interim analysis.[7] As might be expected, patients on sunitinib (for whom median treatment duration had nearly doubled) experienced a comparative increased frequency in overall adverse events.

The most commonly reported sunitinib-related grade 3 adverse events included hypertension (12%), fatigue (11%), diarrhea (9%), and hand-foot syndrome (9%). None of these adverse events occurred with grade 4 severity. The predominant grade 3 or 4 laboratory abnormalities were neutropenia, lymphopenia, and increase in lipase (all 18%) for the sunitinib group and lymphopenia (26%) for the IFN-α group.[7]

Decline in left ventricular ejection fraction is a recognized adverse event associated with sunitinib. In the phase 3 our study, 13% of patients had a sunitinib treatment-related adverse event of ejection fraction decline as reported by investigators, including 3% with grade 3 severity. When compared with its previously reported incidence from the interim analysis (10% all grade; 2% grade 3), these data do not suggest a cumulative effect with long-term sunitinib treatment.

Sorafenib

Sorafenib tosylate (Nexavar®) is an orally active multikinase inhibitor that blocks VEGFR-2, VEGFR-3, and PDGF receptor β (PDGFR-β), as well as RAF-1, Flt-3, and c-KIT.[21]

Sorafenib is a potent inhibitor of Raf-1, a member of the RAF/MEK/ERK signaling pathway. Additional characterization showed that sorafenib suppresses both wild-type and V599E mutant BRAF activity *in vitro*. In addition, the drug demonstrated significant activity against several receptor tyrosine kinases involved in neovascularization and tumor progression, including vascular endothelial growth factor receptor (VEGFR)-2, VEGFR-3, platelet-derived growth factor receptor β, Flt-3, and c-KIT. In cellular mechanistic assays, sorafenib demonstrated inhibition of the mitogen-activated protein kinase pathway in colon, pancreatic, and breast tumor cell lines expressing mutant KRAS or wild-type or mutant BRAF, whereas non–small-cell lung cancer cell lines expressing mutant KRAS were insensitive to inhibition of the mitogen-activated protein kinase pathway by BAY 43-9006. Potent inhibition of VEGFR-2, platelet-derived growth factor receptor β, and VEGFR-3 cellular receptor autophosphorylation was also observed for sorafenib.[21]

Efficacy. Sorafenib resulted in a longer progression-free survival compared to placebo in patients who had previously received a systemic therapy, which largely consisted of cytokines. The final OS of patients receiving sorafenib was comparable with that of patients receiving placebo (17.8 *v* 15.2 months, respectively; hazard ratio [HR] = 0.88; $P = .146$); however, when post–cross-over placebo survival data were censored, the difference became significant (17.8 *v* 14.3 months, respectively; HR = 0.78; $P = .029$).[21]

Safety profile. Sorafenib was well tolerated, and most AEs were grade 1 or 2, easily managed, and consistent with prior reports. The observed cardiovascular events are more notable than in the original report and are similar to what has been reported with other VEGF pathway–directed agents. Although these events were confounded by the longer treatment time on sorafenib than placebo, they illustrate the potential vascular toxicity of these agents. Whether more aggressive blood pressure management, as has been suggested with increasing experience with VEGF pathway–directed agents, will ameliorate this toxicity remains to be determined. Twenty-two patients (4.9%) randomly assigned to sorafenib reported cardiac ischemic/infarct AEs, with six events reported as related to study drug. Dose interruption was required in six patients receiving sorafenib, and one participant reported dose reduction. One cardiac ischemic event in the sorafenib group led to permanent discontinuation of study drug. Of note, the sorafenib arm had a longer follow-up time and inclusion of postprogression patients.

Pazopanib

Pazopanib (Votrient®) is a potent and selective, orally available, small molecule inhibitor of VEGFR-1, -2, and -3; PDGFR-α, PDGFR-β; and c-kit tyrosine kinases. The agent selectively inhibits proliferation of endothelial cells stimulated with VEGF but not with basic fibroblast growth factor. In preclinical angiogenesis models, pazopanib inhibited VEGF-dependent angiogenesis in a dose-dependent manner, and in xenograft tumor models twice-daily administration of pazopanib significantly inhibited tumor growth in mice implanted with various human tumor cells.[22]

Efficacy. In a phase III trial,[22] of 435 patients enrolled, 233 were treatment naive (54%) and 202 were cytokine pretreated (46%). PFS was significantly prolonged with pazopanib compared with placebo in the overall study population (median, PFS 9.2 *v* 4.2 months; hazard ratio [HR], 0.46; 95% CI, 0.34 to 0.62; $P < .0001$), the treatment-naive subpopulation (median PFS 11.1 *v* 2.8 months; HR, 0.40; 95% CI, 0.27 to 0.60; $P < .0001$), and the cytokine-pretreated subpopulation (median PFS, 7.4 *v* 4.2 months; HR, 0.54; 95% CI, 0.35 to 0.84; $P < .001$). The objective response rate was 30% with pazopanib compared with 3% with placebo ($P < .001$). The median duration of response was longer than 1 year.

Safety profile. Diarrhea, hypertension, hair color changes, nausea, anorexia, and vomiting were the most commonly reported AEs (incidence of ≥ 20%).[22] Most AEs related to pazopanib treatment were grade 1/2 and were clinically manageable. The most common grade 3/4 AEs were hypertension and diarrhea. The most common grade 3/4 chemistry abnormalities were ALT elevation and AST elevation. Most cases of drug-induced liver enzyme elevations were asymptomatic and occurred within the first 4 months of treatment. Certain AEs known to occur with this class of agents, including proteinuria, thrombocytopenia, hypothyroidism, hand-foot syndrome, and mucositis/stomatitis, occurred with an incidence of fewer than 10% each, with grade 3/4 events reported in less than 1% of patients. Although some AEs observed with pazopanib are related to target inhibition, others may result from off-target activity. Potential dif-

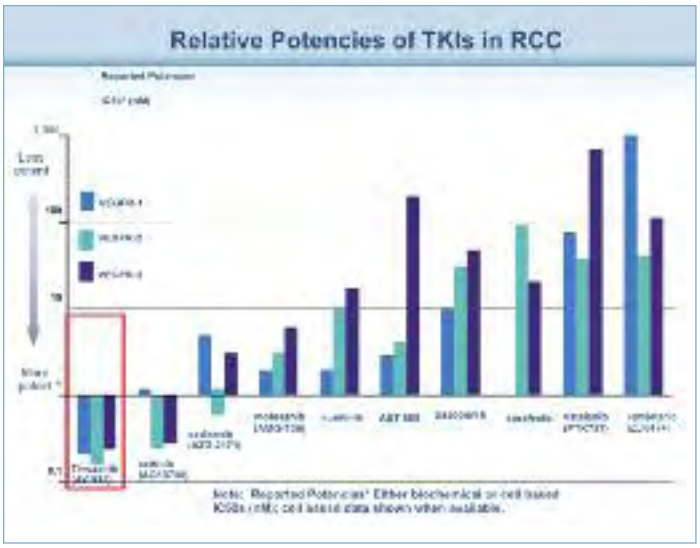


Figure 1. Inhibition of vascular endothelial growth factor receptors. Tivozanib and axitinib show more potential inhibition than other agents.

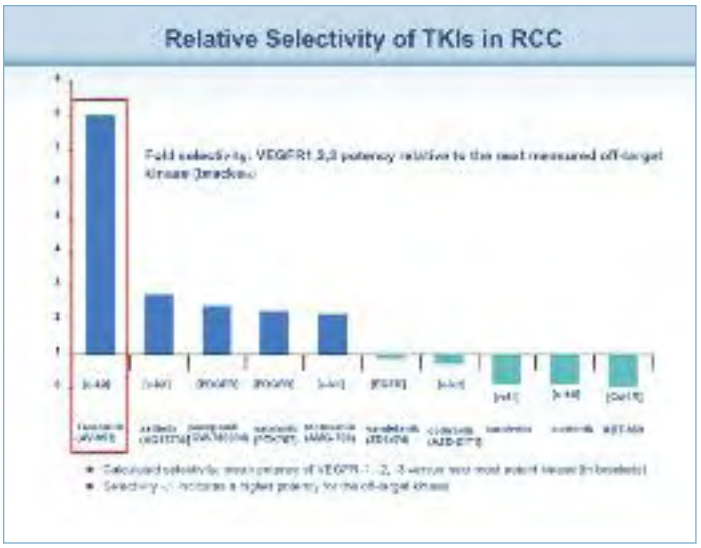


Figure 2. Relative selectivity of various agents for off-target kinase c-KIT.

ferences in the safety profiles of multikinase angiogenesis inhibitors may be explained by differences in the potency and selectivity of kinases inhibited.[22]

The Next Generation of Targeted Therapies

VEGF blockade will remain one of the principal pathways of inhibition in the future, and but a key issue is to what extent the newer TKIs will replace the first generation of TKIs, including sunitinib and, sorafenib, asd and pazopanib will well as successful to be the drugs that build into future combinations. The limitations of the earlier developed shortcomings of these agents are apparent. One aspect in and part of the development of the new VEGF pathway inhibitors is not just the discovery of "cleaner" inhibition of the VEGF pathway. A second is to identify agents that target additional pathways important for acquired resistance to VEGF pathway inhibitors, i.e. contributing to angiogenic escape. In both instances, there is a need for oral administration which can allow for combination studies to be done a little more easily than they were with sunitinib or sorafenib. If more selective therapies can become part of the decision tree, we also need to address the issue of off-target toxicities and whether these newer agents provide a more acceptable safety profile.

Tivozanib

Tivozanib could be considered as athe prototype of the next generation of targeted therapies that are highly selective for the VEGF pathway. It is a potent and selective small-molecule inhibitor of the VEGFR 1,2, and 3 kinases at subnanomolar concentrations (IC_{50} of 0.21, 0.16, and 0.24 nM, respectively.[23] Data from phase 1 and phase 2 trials have demonstrated why this agent is looked upon as a one of the most promising new of the next generation of TKItargeted therapies. In a phase 1 study, tivozanib demonstrated:

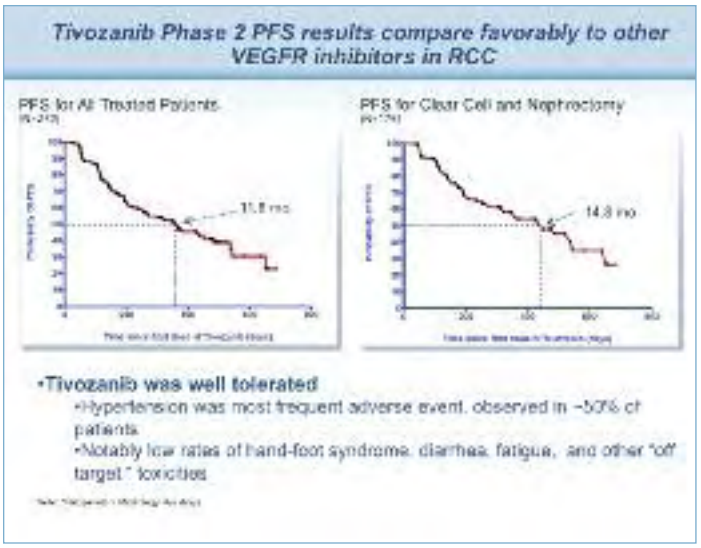


Figure 3. Comparison of progression-free survival of tivozanib vs other VEGF inhibitors.

- a maximum tolerated dose to be 1.5 mg/day
- promising clinical activity in multiple tumor types
- 9 patients with RCC,2 achieved a partial response and 7 had stable disease (6 of 7 for at least 3 months).
- Hypertension was the most frequently observed adverse event.

Targeting profile and RCC. The relative potencies of TKIs in RCC suggest why tivozanib is a highly selective inhibitor of VEGFR-1, -2, and 3, and may be significantly more potent than most of the other drugs in this class. (**Figure 1**) VEGF receptor-1 is crucial for the modulation of endothelial cell survival and vessel morphogenesis. VEGF receptor 2 is thought to be the predominant receptor for endothelial cell proliferation and migration. VEGF receptor-3 promotes endothelial

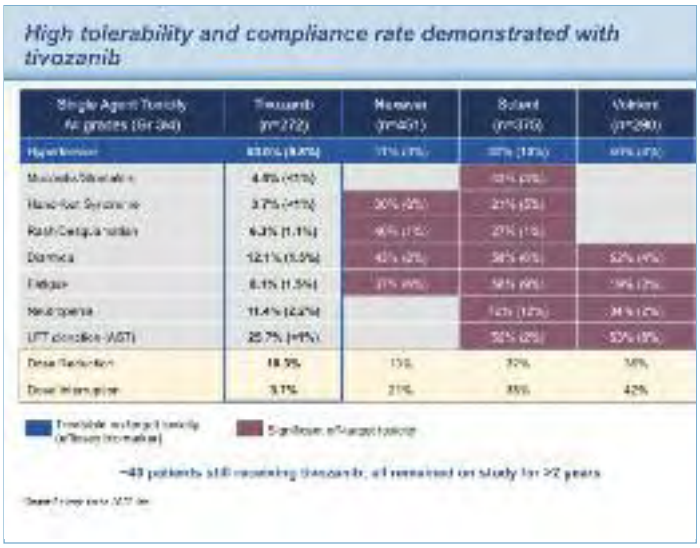


Figure 4. Safety data for the new TKI tivozanib.

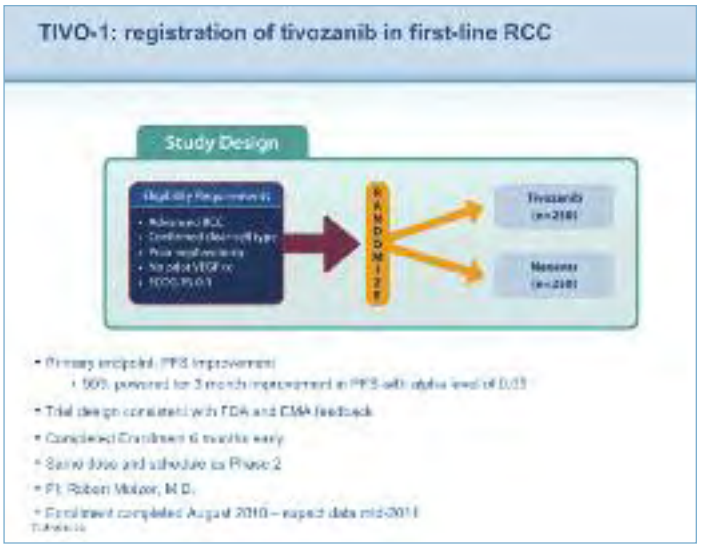


Figure 5. A new trial will examine tivozanib as first line-therapy in RCC.

sprouting and vascular network formation. The relative selective profile of tivozanib compared with other agents is significantly greater (**Figure 2**). In this case, a selectivity of less than 1 indicates a higher potency for the off-target kinase. Tivozanib also exhibits a significantly greater terminal half life of 4.5 days and the advantage of once-daily oral dosing.[23]

Efficacy. Tivozanib has been evaluated in a "randomized discontinuation" phase II study of patients with metastatic RCC who had not received prior VEGF-targeted therapy. Data from this trial were updated at the 2010 American Society of Clinical Oncology (ASCO) meeting and revealed that ORR was achieved in 27% of 245 evaluable patients and PFS was 11.8 months overall. Restricting the analysis to patients with clear cell histology who underwent prior nephrectomy (N=176, 72% of the population), median PFS was 14.8 months. Activity of tivozanib (AV-951) in patients with renal cell carcinoma (RCC): Subgroup analysis from a phase II randomized discontinuation trial (RDT).[24] The median duration of treatment in the trial was 8.5 months (range, 0.03-23.8) (**Figure 3**).

Safety profile. The 272-patient Phase 2 randomized discontinuation trial demonstrated the following:

- Hypertension was the most common treatment-emergent adverse event, reported by 50% of patients. Development of systolic hypertension (>140 mm Hg) or diastolic (>90 mm Hg) hypertension during therapy was associated with significantly improved PFS (*P*=0.01).[24]
- The side effect profile of tivozanib was notable for a low incidence of off-target toxicities: fatigue (8.1%), stomatitis (4.4%; no grade ¾), and hand-foot syndrome (3.7%; no grade ¾).
- Dose reductions due to adverse events were required by 10.3% of patients.
- Treatment interruptions de to adverse events were required by 3.7% of patients (**Figure 4**).

The TIVO-1 Phase 3 Trial

Accrual has been completed for the TIVO-1 Phase 3 head-to-head trial of tivozanib vs sorafenib as initial targeted therapy in patients with metastatic RCC. Results are expected by the end of 2011 This will be the first head-to-head RCC registration trial of tivozanib vs an active comparator. The primary end point is PFS with secondary endpoints of overall survival, response rate, and quality of life. The treatment schedule for tivozanib will be 1.5 mg/day for 3 weeks followed by a 1-week break. For sorafenib the schedule will be 800 mg/day for 4 weeks (**Figure 5**).

Axitinib

Axitinib is an oral, potent, and selective inhibitor of VEGFRs 1, 2, and 3 that has shown substantial activity in a phase II trial in patients with cytokine-refractory mRCC;[1] its demonstrated activity included an objective response rate (ORR) of 44%, a median time to progression of 15.7 months, and a median overall survival (OS) of 29.9 months.[1] Given that axitinib is more potent and selective against the VEGFR family compared with sorafenib and sunitinib in biochemical assays and that a lack of complete cross resistance to antiangiogenic therapies has been seen in mRCC, it was hypothesized that axitinib may provide clinical benefit in patients who had received prior VEGF-targeted therapy. A phase II study investigated the activity of axitinib in patients with mRCC after failure of sorafenib and, often, additional therapies as a result of progression or unacceptable toxicity.

Efficacy. Of 62 patients recruited, 100% had received prior sorafenib, and 74.2% had received two or more prior systemic treatments. The axitinib dose was titrated to greater than 5 mg twice daily in 53.2% of patients, and 35.5% of patients had the dose modified to less than 5 mg twice daily. In 62 patients evaluable for response, the ORR was 22.6%, and the median duration of response

was 17.5 months. Median PFS and OS times were 7.4 months (95% CI, 6.7 to 11.0 months) and 13.6 months (95% CI, 8.4 to 18.8 months), respectively. All-causality grade 3 to 4 adverse events included hand-foot syndrome (16.1%), fatigue (16.1%), hypertension (16.1%), dyspnea (14.5%), diarrhea (14.5%), dehydration (8.1%), and hypotension (6.5%).

The precise mechanism of axitinib activity after the failure of sorafenib or other antiangiogenic agents remains to be definedis unclear. It may be related to the high selectivity and subnanomolar potency of axitinib for VEGFRs 1, 2, and 3, which contrasts with inhibition constants in the nanomolar range for sunitinib and sorafenib. Alternative hypotheses include increased susceptibility to VEGF-targeting as a result of the washout period between therapies and variability in absorption between compounds that affect active drug levels. Nonetheless, this study and prior data support the sequential use of targeted therapies in the face of clinical progression.

Safety profile. The safety profile of axitinib was consistent with previously reported findings,except, except for a higher incidence of hand-foot syndrome in this trial and more skin toxicities in the study of axitinib in cytokine-refractory RCC by Rixe et al. Dose reductions occurred to a greater extent in this study compared with the cytokine-refractory RCC study, but they were due to comparable AEs. The impact of prior therapy on subsequent toxicity with axitinib requires additional study. Hand-foot syndrome was more common in patients in this study who received at least one total daily dose of axitinib greater than 10 mg (19 [57.5%] of 33 patients) than in patients who did not (three [10.3%] of 29 patients). This syndrome is a characteristic toxicity of multitargeted TKIs.Fatigue, diarrhea, hypertension, and anorexia were the most commonly reported AEs, whereas hematologic AEs were relatively rare. Most AEs were manageable by dose reductions or interruptions and by standard medical intervention. The occurrence of hypertension (ie, diastolic BP ≥ 90 mmHg) has been associated with superior OS, PFS, and ORR in a combined analysis of patients from this study and another phase II study of RCC. Hypothyroidism has been reported in patients receiving axitinib,[26] and 29.0% of patients in this study received levothyroxine while on study.

Dovitinib

Dovitinib (TKI258) is one of two new targeted therapies that also target the FGFR pathway which has been reported as an important escape mechanism of anti-VEGFR therapies. Activating mutations or overexpression of fibroblast growth factor receptors (FGFRs) or their ligands have been associated with neoplastic progression and tumor vascularization in multiple cancer types, including breast cancer, bladder cancer, multiple myeloma, hepatocellular, and renal cell carcinoma. Dovitinib, orally bioavailable, has demonstrated inhibition of VEGFR and FGFRs in clinical trials.

Efficacy. A phase 1 study determined the MTD and preliminary activity of TKI258, administered p.o. on a 5-day on/2-day off schedule in a repeated 28-day cycle, in mRCC pts refractory to standard therapies.[25] Patients were treated with 500 mg (n=15) or 600 mg (n=5) TKI258 qd doses.[25] Confirmed partial response (PR) occurred in 2(10%), stable disease (SD) in 7(35%) and disease progression (PD) in 8(40%). Preliminary median progression free survival was 5.5 months (range 1- 446+ days). In a subset of 10 pts previously treated with VEGFR TKI and mTORi, 1 confirmed PR was reported, and 6 SD and 2 PD observed at week 16. Patients (n=20) had high baseline VEGF and bFGF levels, which may reflect failure of previous anti-VEGF agents. In patients treated at 500mg: plasma FGF23 levels increased 53% over baseline indicating FGFR1 inhibition, VEGF and PLGF increased 107% and 23%, respectively, sVEGFR2 decreased by 21%, and IHC of a paired tumor biopsies showed significant decrease in pERK expression and microvessel density at day 15 of TKI258 treatment.

Safety profile. The most common adverse events were nausea (80%; G3:5%), diarrhea (70%), vomiting (65%), asthenia (50%; G3:15%), anorexia (45%; G3:5%), headache (30%; G3:5%), hypertension (25%; G4:5%), and rash (23%; G3:5%.

TKI258 MTD was defined as 500 mg qd for the schedule tested. TKI258 was well tolerated and encouraging antitumor activity was observed in heavily pretreated patients. Phase II part of the study is ongoing and a randomized phase III study is underwayplanned in patients previously treated with VEGFR TKI and an mTORi.

E7080

E7080 is a potent, orally administered, receptor tyrosine kinase inhibitor of KDR, VEGFR1, VEGFR3, FGFR2, and RET. Antiangiogenic and antiproliferative activity have been reported in human cancer xenograft models, suggesting that E7080 may be a promising anticancer agent. (***Editor's note:*** Additional data on the potential use of E7080 in RCC are expected later this year and will be reviewed in a subsequent issue of the *Kidney Cancer Journal*.)

Conclusion and Future Directions

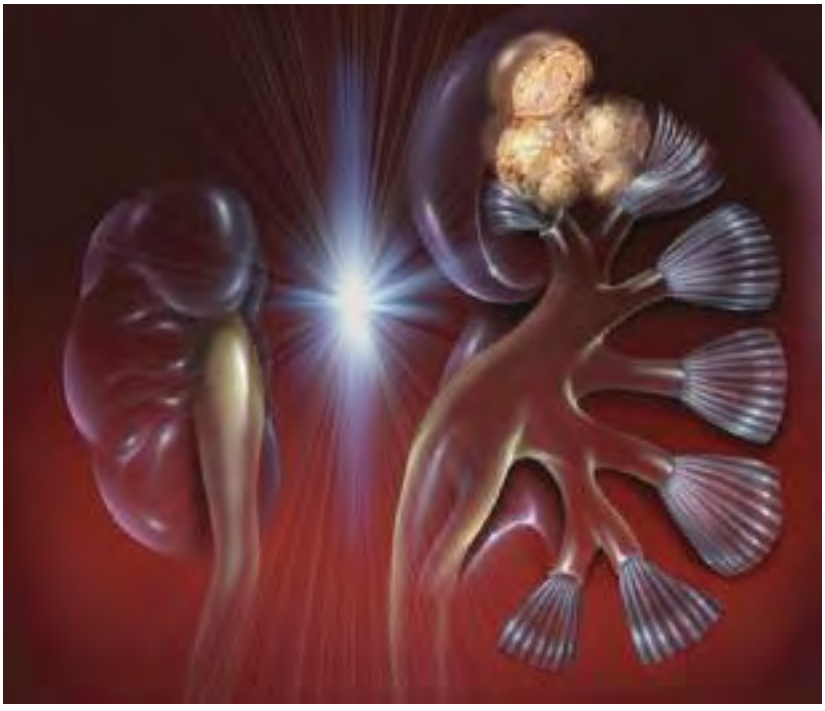
The future is promising for further advances in therapeutic options for metastatic RCC, as bright for new targeted therapies in RCC, with several drugs completing accrual or moving toward promising phase 3 trials. These drugs include tivozanib, axitinib, dovitinib and E7080 and could provide further advance in help resolve a significant unmet need for RCC management. This new generation of targeted therapies will hopefully provide expanded treatment options, including more selective or "cleaner" inhibition of the VEGF pathway, an improved side effect profile and prolonged progression free survival compared to the first generation of TKIs. As the spectrum of therapy expands with these agents, we

(continued on inside back cover)

SPECIAL FEATURE

Revisiting High-Dose IL-2 Therapy:

Three Challenging Cases in RCC



Tumor in the upper pole is beginning to impinge on the pyramids and calyces in a conceptual illustration of the use of ablation in renal cell carcinoma.

Supported by a grant from Prometheus Laboratories Inc.

High-Dose Interleukin-2 in the Evolving Immunotherapy Landscape for Metastatic Renal Cell Carcinoma: Three Cases

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With an annual incidence exceeding 200,000 worldwide, kidney cancer is the cause of more than 100,000 deaths around the world each year.[1] In the United States, an estimated 58,240 people were expected to be diagnosed with renal cell carcinoma (RCC) in 2010, and more than 13,040 were expected to die from the disease last year.[2] Renal tumors comprise approximately 3% of adult malignancies, and are 1.6 times more common in men than in women.[3] Nineteen percent of patients with RCC are diagnosed after the cancer has metastasized, and metastases will develop in 20% to 40% of individuals undergoing nephrectomy for localized RCC.[2,4] Historically, patients with recurrent and/or metastatic RCC (mRCC) have had a poor prognosis, as reflected by a median survival of 10 to 13 months and 5-year survival rates of less than 5%.[5-7]

Chemotherapy has limited activity in this population, and though interferon-α (IFN-α)-based therapy is associated with marginal survival benefits, response rates are modest (5%-15%) and responses are of limited duration.[8,9] The recent advent of drugs targeted to the vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) pathways has led to improvements in disease control and overall survival but no cure for mRCC, and at the cost of chronic adverse effects.[10,11] Hence there is a need for more effective and durable systemic therapies for patients with mRCC that maintain or enhance quality of life.

Use of High-Dose Interleukin-2

Interleukin-2 (IL-2) is one of a group of cytokines that mediate signals between cells during an immune response. An autocrine T cell growth factor produced by T cells, IL-2 stimulates T cell secretion of tumor necrosis factor and other cytokines such as IL-4 and interferon-γ, potentiating the proliferation and activation of T cells, including cytotoxic T lymphocytes, and natural killer and lymphokine-activated killer cells.[12] High-dose bolus aldesleukin, a recombinant form of IL-2, was approved by the US Food and Drug Administration (FDA) in 1992 for the treatment of patients with mRCC based on data from 7 phase 2 studies involving 255 patients. In these trials, objective responses were observed in 15% of patients, including complete responses (CRs) in 7% and partial responses (PRs) in 8%. The median duration of response was 54 months for all responders, 20 months for those achieving a PR, and has not been reached for complete responders. The median survival for all 255 patients was 16 months.[13] More contemporary data from the Cytokine Working Group (CWG) SELECT trial in 120 evaluable patients show CRs in 6% and PRs in 22%, with 12% having stable disease (SD).[14]

High-dose IL-2 induces a complete remission in some patients with mRCC, and is the only FDA-approved agent that can produce a complete and durable response.[15] Adverse events with IL-2 are generally acute, predictable, manageable, and reversible, allowing patients to recover and maintain a relatively good quality of life outside of the treatment window, compared with more chronic treatments.[16-18] In addition, response to IL-2 is determined relatively quickly, with most responders identified after one course of therapy.[19] First-line IL-2 therapy for mRCC may therefore preserve the clinician's ability to pursue subsequent treatment options, as suggested in a recent phase 2 study of sunitinib plus erlotinib for advanced RCC, in which the 10 patients given prior high-dose IL-2 had a progression-free survival of 15.3 months, compared with 5.1 months for the 27 patients with no prior cytokine therapy.[20]

Selecting Appropriate Candidates for High-Dose IL-2 in an Evolving Treatment Landscape

Although cytokine therapy was the standard of care for mRCC for about 15 years, inhibitors of VEGF and mTOR—a group of agents that includes the tyrosine kinase inhibitors sunitinib, sorafenib, and pazopanib, as well as temsirolimus, everolimus, and bevacizumab—have in recent years become widely used as a form of targeted therapy.[21] Whereas the relatively favorable toxicity profiles of the targeted agents make them attractive to many clinicians and patients, these agents generally require lifetime compliance in the face of chronic adverse effects, and have not generated responses as durable as those reported with IL-2.[18,22]

The limitations of targeted therapy have thus refocused attention on IL-2 and other immunotherapeutic approaches. Although there is some debate about the utility of various criteria for selecting appropriate candidates for IL-2 therapy, the best criteria are largely based on safety and include the patient's performance status,

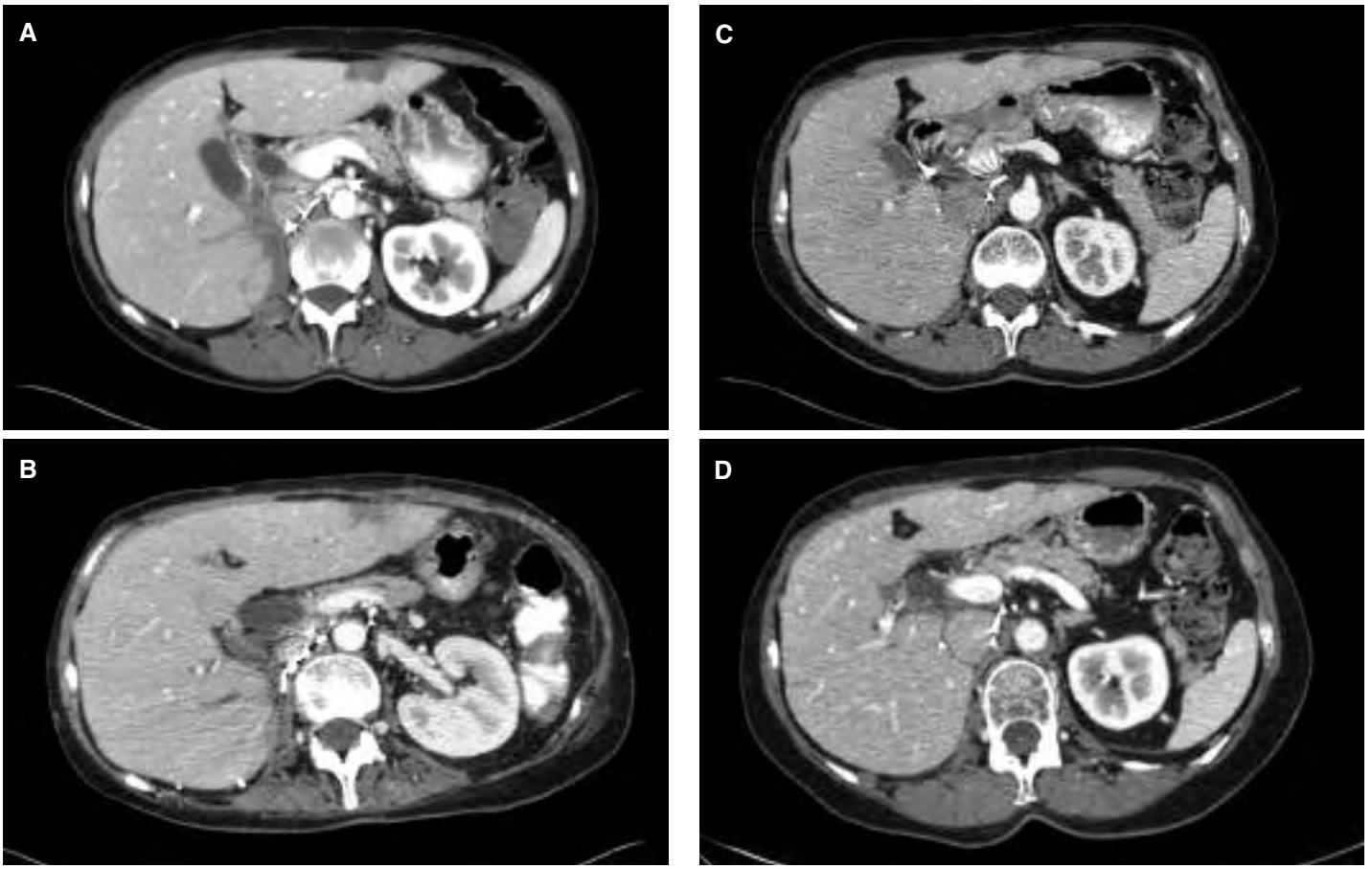

Figure 1, CASE 1. Computerized tomography of the upper abdomen with intravenous contrast taken before (A), during (B) and after (C) high dose interleukin-2 therapy and at 7 year follow-up in 2011 (D). The patient's left lobe of liver metastasis decreased in size and contrast enhancement progressively during HD IL-2 to leave a low density defect on CT scan.

medical comorbidities, tumor histology (predominantly clear cell with alveolar features), risk stratification tools (such as those developed by Memorial Sloan Kettering Cancer Center [MSKCC] and the University of California Los Angeles), and the patient's own attitude toward risk.[7,21,23,24] In general, adult patients with Eastern Cooperative Oncology Group performance status scores of 0 or 1 have the best chance for a complete and dur-able response to high-dose IL-2, with the least toxicity.[13]

Other patient selection criteria include normal central nervous system (CNS) function and absence of CNS metastases; normal cardiac, pulmonary, and hepatic function; absence of organ allografts; and absence of active infection or autoimmune disease.[25] Most candidates for high-dose IL-2 therapy have pulmonary metastases and are considered a good risk, according to the MSKCC prognosis criteria.[7] Although the MSKCC criteria can help select likely responders to IL-2 therapy based on "good" predictive features, they should not be the only criteria. The recent CWG data indicate that clear-cell histology appears better able to select such responders, which suggests that some patients with poor or intermediate prognoses may benefit.[14] The following 3 cases provide examples of complete, partial, and nonresponses to high-dose IL-2.

■ CASE 1: Complete, Durable Response to High-Dose IL-2 Therapy

Patient presentation and history

The patient was a 55-year-old white woman with a history of cigarette smoking (30 pack-years), she had quit smoking roughly 3 years before presenting at our clinic. She was evaluated after a referral from her urologist, who had performed a right radical nephrectomy and thrombus resection following a diagnosis of clear-cell renal cell carcinoma. Within 6 months of that surgery, the patient experienced a return of the cancer, as evidenced by metastases in her liver and lung.

Patient assessment. The patient underwent stress testing and pulmonary function testing, neither of which was abnormal. Magnetic resonance imaging (MRI) of the brain and a technetium bone scan were negative for metastases.

Treatment and outcomes. The patient underwent 3 courses of high-dose IL-2 (aldesleukin) therapy as per the National Cancer Institute (NCI) treatment protocol for RCC (600,000 IU/kg every 8 hours, via 15-minute infusions). She had an incremental response to each course, and the first 2 courses were well tolerated. The first course, starting in February 2004, consisted of 14 doses over the first week and 12 doses over the second week.

For the second course of treatment, which was administered in May 2004, the patient received 13 doses over the first week and 8 doses over the second week. The patient experienced major edema, lethargy, and skin peeling with each course but recovered rapidly. Although there was no evidence of lung metastasis after the second course, there was a residual liver metastasis measuring 4.1 x 2.5 cm; the liver mass had shrunk to 2.8 x 1.4 cm upon later reexamination. A subsequent scan revealed no change to the liver mass and no residual lung disease.

We initiated the third course of IL-2 therapy in August 2004. This course was reasonably well tolerated for the first week, during which 9 doses were administered. However, the second week of this course was not initiated because the patient had developed septicemia and a spontaneous small bowel perforation. She was treated with antibiotics and had 2 laparotomies for the small bowel perforation. Initially, repair with over-sew of the perforated bowel was attempted but at the second surgery multiple perforations were seen and the abdomen was not closed. The patient was nursed with an open wound for 2 weeks and discharged home with an open abdominal wound, which was managed with a "wound vac"; the wound healed within 6 weeks. Whereas IL-2 therapy is more commonly associated with large bowel colitis, the occurrence of non-specific small bowel colitis in this case was considered unusual.

The patient was scanned 12 weeks after completion of the third course of therapy. There was no evidence of liver metastasis at that time; the cancer has been in complete remission since then. Five years after completing IL-2 therapy, the patient returned to the clinic with hematuria, and was diagnosed with high-grade superficial bladder cancer, which was not considered a recurrence of her RCC. She was treated with transurethral resection of the bladder and bacillus Calmette-Guérin chemotherapy. Nearly 2 years later, the patient has remained clear of disease.

■ CASE 2: Partial Response to High-Dose IL-2 Therapy

Patient presentation and history

The patient, a 57-year-old black man receiving treatment for chronic hypertension, was referred to our clinic for assessment for systemic therapy for mRCC. He had undergone a left nephrectomy for clear-cell RCC (T2 N0 lesion) 9 years earlier; lesions were detected in his lungs and mediastinum 8 years after this procedure. In June 2003, 1 year before his referral to our clinic, the patient was hospitalized for pneumonia, and received a computed tomography (CT) scan that revealed subcarinal lymph node metastases as well as 5 bilateral lung nodules in the parenchyma. In May 2004, the patient underwent a mediastinoscopy, including biopsy of a mass in his mediastinum, which confirmed the presence of metastatic renal clear-cell carcinoma.

Patient assessment. As part of his workup in July 2004, the patient underwent stress testing and pulmonary function tests, neither of which were abnormal. Two pancreatic lesions were detected via CT scanning. An MRI of the brain disclosed the presence of an asymptomatic hypervascular metastasis, measuring 11 mm, on the left frontal lobe; this lesion was treated with stereotactic radiosurgery. Three months later another MRI showed significant regression of the lesion.

Treatment and outcomes. In November 2004 we initiated treatment with high-dose IL-2 according to the NCI protocol. The patient received 11 of the planned 14 doses during the first week of the first course of therapy. Although treatment was discontinued due to elevated serum creatinine levels (3.7 mg/dL), it was otherwise well tolerated by the patient. A total of 8 doses were administered over the second week of the first course, which was discontinued because of hypotension, fluid retention, and pulmonary edema.

A CT scan administered in early February 2005 revealed stable disease, prompting a second course of therapy. The patient received 9 doses over the first week, after which treatment was stopped because of hypotension and tachycardia. Seven doses were administered over the second week of the second course. In March 2005, an MRI of the brain revealed further resolution of the frontal lobe lesion. Further scanning showed an increase in the size of the patient's peritoneal nodes, unchanged upper mediastinal nodes, and growth in one of the pancreatic lesions from 12 to 22 mm.

In June 2005, after continued observation and a repeat MRI scan, we determined that the patient had further disease progression and we decided to administer a different course of therapy. At that point the patient commenced treatment with imoxine, an immunostimulatory agent, as part of a clinical trial. He remained on imoxine therapy for more than one year, during which time a metastasis was detected in the patient's lung. He was then initiated on sorafenib therapy (off-study), and remained on this regimen for more than 3 years, whereupon he experienced progressive disease and switched to everolimus therapy, which he continues to take.

■ CASE 3: Nonresponse to High-Dose IL-2 Therapy

Patient presentation and history

The patient was a 47-year-old white man referred to our clinic by his community oncologist. We first saw him in March 2009, when he presented with multiple bilateral pulmonary metastases, and reported left upper quadrant pain, weight loss of 14 pounds over 3 months, and night sweats. He also reported a palpable mass in the left upper quadrant area.

Patient assessment. In May 2008, the patient had undergone surgery to remove a mass from his left kidney measuring 10 cm across, extending into the pelvis. The mass was determined to be clear-cell RCC with associated necrosis. All margins were free. Three months after the surgery, subpleural nodules were detected; these

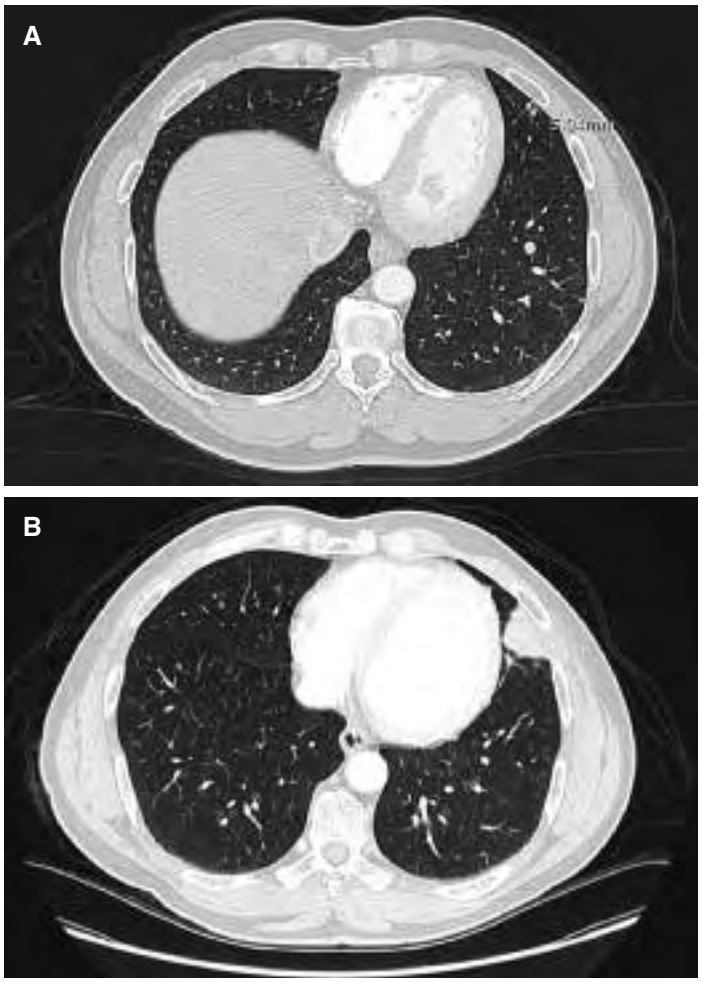

Figure 2, CASE 3. Computerized tomography of the lower thorax showing a 5mm diameter lesion in the left lower lobe before HD IL-2 therapy (A). The patient developed multiple lung metastases within a year of nephrectomy for a renal clear cell cancer with some associated necrosis but no sarcomatoid elements reported or found on review at our center. The lesion in the left lower lobe continued to grow despite reduction in volume and decreased density of other lung lesions on HD IL-2, sorafenib on clinical trial then sunitinib (B). Thoracoscopic evaluation of the lesion revealed pleural studding and diaphragmatic involvement that precluded resection. Biopsy revealed sarcomatoid differentiated renal cell cancer in this resistant nodule.

were monitored until February 2009, when a CT scan revealed multiple new lung parenchymal nodules up to 10 mm in diameter. The patient reported no previous history of tobacco use and had no significant comorbidities. Aside from the cancer he was in good health.

Treatment and outcomes. We initiated high-dose IL-2 therapy in late March 2009, with dosage determined by the NCI protocol. The first course, which consisted of 14 doses over the first week and 10 doses over the second week, was well tolerated, though treatment was stopped before completion of the second week because of treatment-related lethargy and fluid retention. A follow-up scan in May 2009 showed what was described as a mixed response to therapy; whereas some nodules had shrunk, particularly the left pleural and neurolingual nodules, the remaining nodules had slightly increased in size (ie, by roughly 1 mm). The right hilar node was found to be enlarged (14 mm); although we were unsure of the prognostic significance of this enlargement—it is not uncommon for node size to increase or decrease after IL-2 therapy.

The patient elected to receive a second course of IL-2 therapy in June 2009. He received all 14 planned doses during the first week, and 11 of 14 doses in the second week. A subsequent scan 2 months later showed a significant increase in size of a lesion in the left pleura; although this lesion had initially shrunk, the scan showed it had more than doubled in size. Smaller increases were observed in other lung nodules.

At that point, we determined that the lack of a definitive response made the patient a good candidate for the AXIS trial, which compared sorafenib to axitinib as second-line therapy. The patient enrolled in the trial in September 2009 and was randomized to sorafenib. He remained on sorafenib for approximately 12 months, whereupon he was determined to have progressive disease with an increase in the size of the left pleural lesion that had grown after the second course of IL-2 therapy. Although the size of the patient's lung disease had decreased while on sorafenib, this was not considered a partial response. The patient was switched to sunitinib therapy, and subsequently experienced slight shrinkage of most lung lesions, except for the left pleural lesion, which now measured roughly 4 cm in diameter. The patient was referred to a thoracic surgeon and excision is planned.

Discussion

High-dose IL-2 provides an important treatment option for selected patients with mRCC.[14,26] Its broader use may herald a renaissance in cancer immunotherapy along with agents such as sipuleucel-T and ipilimumab, which were recently approved by the FDA for the treatment of prostate cancer and melanoma, respectively.[27,28] Whereas various targeted therapies and chronic low-dose cytokine regimens may result in disease control in mRCC, none has thus far produced the consistent, durable complete response rate seen with IL-2.

The first case in this series is notable in that it demonstrates that a patient with liver metastasis and slow response to high-dose IL-2 therapy can attain a CR that is durable. Although anticancer therapy is often initiated with the goal of a CR, the second case in this series demonstrates that patients who achieve a PR derive some benefit from IL-2 therapy.[13] Despite the lack of a CR, the patient in this second case has achieved good disease control, and has lived with his disease longer than expected, particularly given the presence of brain metastases before initiation of IL-2 therapy. The use of stereotactic radiosurgery, high dose IL-2, and targeted agents has transformed the survival and functional status for a group of mRCC patients with brain metastases, whose survival historically was limited to less than 6 months.[29-31]

The second case is supported by the recent CWG data, which suggest that PR or even SD may be reasonable aims for some patients, in that such patients experience better outcomes than patients with progressive disease.[14] The patient in this case probably fits within that group. Although he experienced some long-term adverse effects related to the subsequent treatments he has received, he has coped with those effects reasonably well.

Although IL-2 therapy did not produce a definitive response in the third case, the treatment was well tolerated, and the patient emerged with essentially stable disease. Whereas the left pleural lesion continued to grow, its growth initially appeared to be controlled by the other therapies administered to the patient while the other lesions had shrunk slightly with each treatment given. After 3 lines of therapy, the left pleural lesion appeared to have a different "personality" from the rest of the cancer, which had been controlled with sorafenib and then sunitinib. Notably, the lesion was never biopsied, as the patient's HMO would not approve the procedure despite the risks of the presence of a different cancer or dedifferentiated RCC. Resection of the lesion is now approved and planned.

Immunotherapy represents an important therapeutic opportunity for mRCC patients. Recent experience shows that high dose IL-2 can be given safely to many patients in moderate-volume centers with significant experience.[14] In addition, patients who do not achieve a CR from high-dose IL-2 may still benefit from this treatment. Other data suggest that high-dose IL-2 may not be as safe or efficacious if reserved for second-line or later therapy.[32] The challenge remains in selecting appropriate patients for this important treatment option.

Images courtesy of Vinay Duddalwar, MD FRCR, Section Chief, Abdominal Imaging, USC Norris Hospital and Clinics

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TKIs and the Immune Response: Is There Potential for Combination Therapy?

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A multitargeted tyrosine kinase inhibitor (TKI) may be an important adjunct to reverse immune suppression. Results are still preliminary but recent studies provide better delineation of the tumor microenvironment, with evidence why this drug in combination with immunotherapy could be a candidate for the treatment of metastatic renal cell carcinoma (mRCC).

There are promising signs that an immune-based approach to treating kidney cancer may be on the verge of a breakthrough, renewing interest for immunotherapy after a decades-long effort to improve overall long-term survival with this approach. A new focus, emerging over the past few years, is on immune dysfunction—the tumor microenvironment—how it contributes to tumor evasion and how the antitumor activity of select TKIs, notably sunitinib (Sutent®) could be effectively combined with immunotherapy in mRCC.

An important perspective seen in recent articles concerns the role of myeloid-derived suppressor cells (MDSCs), increasingly recognized for their ability to promote tumor growth by suppressing immune response, and, at least in mouse models, promote angiogenesis, a key factor that enables a tumor to take advantage of the vasculature.[1,2] The immune dysfunction in RCC has been well described.[3-6] There is a shift from a type-1-mediated $CD4^+$ T cell response producing interferon (IFN)-γ, to a type-2 cytokine response that is important in mediating humoral immunity.[7,8] As the process of immune dysfunction becomes clearer, new reports emerge that provide an improved understanding of the immunomodulatory aspects of RCC. These are among the trends reflected in studies of the TKI, sunitinib, within the last 3 years:

- An improved type-1 cytokine response following sunitinib treatment is evident in RCC patients but so far is independent of either tumor shrinkage or objective clinical responses
- MDSC that accumulate in tumor bearing host were shown to be reduced
- The number of immunosuppressive T-regulatory (Treg) cells have been shown to be reduced
- Some of the targeted receptors and signaling pathways have been identified
- Sunitinib combined with different forms of immunotherapy has been tested

Sunitinib Modulation of Immune Cell Responses in RCC Patients

Although it is tantalizing to speculate on the translational impact of the new findings on clinical practice, the data must be viewed cautiously as one of the first steps toward a time when a TKI can perhaps enhance the effectiveness of immunotherapy. Nevertheless, recent literature provides clues as to how this might take shape. Our study gathered data from 42 patients with mRCC. The findings demonstrated that after one cycle of sunitinib treatment there was a significant increase in the percentage of IFNγ-producing T cells (type-1), which is typically diminished in RCC patients relative to the type-1 response of normal healthy donors (**Figure 1A**). This increase in type-1 response was accompanied by a

Keywords: Metastatic renal cell carcinoma, tyrosine kinase inhibitors, myeloid-derived suppressor cells, sunitinib

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reduction in interleukin (IL)-4 production (type-2) and a reduced type-2 bias that is known to diminish antitumor immunity (not shown). The restoration of a type-1 T cell response in patients with RCC by sunitinib treatment is relevant because the development of an effective antitumor immune response is dependent on T cell production of IFNγ (type-1 response). Previous work by Kondo and colleagues[9] showed that patients with RCC whose tumor environment is biased toward a type-1 immune response have a more favorable prognosis.

The restoration of a type-1 T cell IFNγ response was also observed in multiple murine tumor models following sunitinib monotherapy, which illustrated the generality of sunitinib's ability to enhance T cell effector function.[10,11] The positive impact of sunitinib on T cells also included normalizing the ability of $CD4^+$ and $CD8^+$ T cells to proliferate in response to stimulation.

There is growing evidence that immunoregulatory cell expansion in cancer patients and murine tumor models contribute to the suppressed T cell response observed in tumor bearing hosts such as patients with RCC. MDSC and Treg cells are the major regulatory cell types that promote immune suppression in cancer.

Treg cells ($CD3^+CD4^+CD25^{hi+}Foxp3^+$) are increased in mRCC patients and sunitinib treatment was found to be reduced in Treg levels (15%) (**Figure 1B**), and this reduction correlated with an increase in IFNγ-producing T cells after 1 and 2 cycles of therapy.[7] Analysis of additional patients following 4 cycles of sunitinib showed a more dramatic reduction in Treg compared with the other cycles (**Figure 1B**), which needs to be confirmed with a larger patient sample size. Treg reduction by sunitinib was observed in multiple murine tumor models, which revealed a potential mechanism for sunitinib-mediated decrease in Tregs. The expansion of Tregs is in part attributable to the conversion of nonsuppressive $CD4^+$ T cells into Treg cells induced by tumor products (eg, transforming growth factor [TGF]β) along with MDSC.[10,12] Sunitinib treatment reduced the induction of Tregs from the $CD4^+Foxp3^-$ T cell population both in cell culture and in vivo.[10,12]

Following up on these results in another report, Ko and colleagues,[13] addressed the question of whether sunitinib reverses MDSC accumulation. An evaluation included 23 patients with mRCC whose peripheral blood levels of MDSC and Treg and T-cell production of IFNγ were assessed before and after sunitinib treatment. The patients had elevated levels of MDSC ($CD33+HLA^{-DR-}$); the neutrohilic population ($CD15^+CD33^+HLA^{-DR-}$) was most dominate. Sunitinib treatment significantly reduced MDSC as measured by flow cytometry analysis.

The effects of sunitinib on MDSC levels has been updated with additional patients and is shown in **Figure 1C** (Finke, unpublished data, 2011). In addition, the reduction in MDSC correlated with a restoration in the type-1 T-cell suppression that is typically diminished in patients with RCC.[13] Moreover, the reduction in MDSC correlated with a reversal of $CD3^+CD4^+$ $CD25^{hi}$ $Foxp3^+$ Treg cell elevation. Findings from the study by Ko and colleagues[13] also suggest that the reduction of MDSC may make a significant contribution to reversing the impaired type-1 response, since removal of MDSC from cultures of patients' peripheral blood mononuclear cells restored T cell IFNγ production (type-1 response).

However, this study, like that reported by Finke and colleagues,[7] found no correlation between changes in any of the immune parameters tested and changes in tumor burden, response to treatment, or survival. Even patients whose tumors progressed during treatment showed a reduction in MDSC with sunitinib treatment. Although our studies failed to find a correlation between the increase in type-1 bias and tumor shrinkage or objective response, this issue requires elucidation in larger studies.

It was observed that the greatest percentage of tumor shrinkage and the achievement of a partial response tended to occur in patients with a lower type-2 bias at baseline. This is consistent with the suggestion that achievement of a partial response is related to a lower type-2 bias at baseline. However, this is currently a hypothesis. Thus, it is possible that the sunitinib-mediated clinical response is influenced by the degree of the type-2 bias at base line. It may be, for example, that the reduction in immune suppression induced by sunitinib is enhanced by a reduced type-2 bias at baseline. Alternatively, clinical response could be influenced by sunitinib-induced antiangiogenic activity or by promoting an innate immune response. This also needs further clarification.

It is also possible that the reduction in immune suppression by sunitinib in the absence of immune stimulus (ie, immunotherapy) may not be sufficient to promote effective T cell mediated tumor regression. Despite the fact that there are many unanswered questions, Ko and colleagues[13] suggest that future immunotherapeutic trials might include MDSC removal as an important part of the protocol, which is supported by other studies in murine tumor models.[10,11,14] The data further develop the rationale for sunitinib-based combination therapy with immunomodulators to enhance antitumor effects and possibly patient survival.

A report by van Cruijsen and colleagues[15] analyzed the effect of sunitinib on myeloid cells in patients with mRCC. The researchers reached a similar conclusion, the results of their data showed a normalization in the myeloid compartment following treatment. These findings were consistent with other studies, which showed that cancer patients have increased levels of MDSC and functionally impaired dendritic cells (DC) hampered DC differentiation has correlated with poor prognosis.[15-17]

Administration of sunitinib (4 weeks followed by a 2-week rest) reduced the increase in MDSC ($CD14^+HLA^-$ DRneg/low). Reduced frequencies of DC subsets pretreatment with a further decline during treatment were also observed, however DC levels recovered to normal at the end of treatment. In addition, Cruijsen and col-

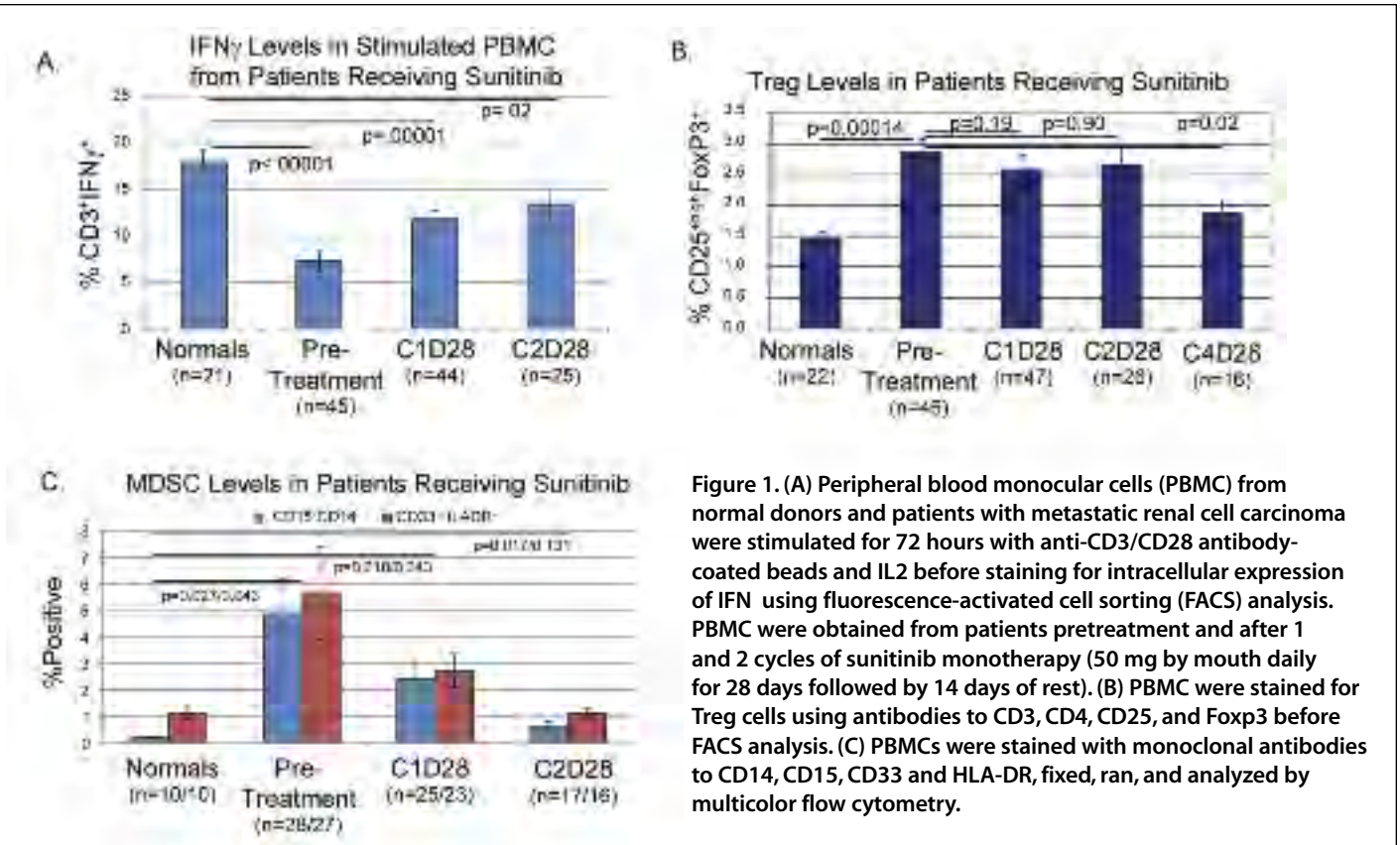


Figure 1. (A) Peripheral blood monocular cells (PBMC) from normal donors and patients with metastatic renal cell carcinoma were stimulated for 72 hours with anti-CD3/CD28 antibody-coated beads and IL2 before staining for intracellular expression of IFN using fluorescence-activated cell sorting (FACS) analysis. PBMC were obtained from patients pretreatment and after 1 and 2 cycles of sunitinib monotherapy (50 mg by mouth daily for 28 days followed by 14 days of rest). (B) PBMC were stained for Treg cells using antibodies to CD3, CD4, CD25, and Foxp3 before FACS analysis. (C) PBMCs were stained with monoclonal antibodies to CD14, CD15, CD33 and HLA-DR, fixed, ran, and analyzed by multicolor flow cytometry.

leagues[15] reported an association between sunitinib-induced tumor regression and an increased frequency at baseline of one DC subset in particular, the CD1c/BDCA-1$^+$ myeloid DC (MDC)$^{-1}$ subset. Additional studies are needed to further define the impact of TKI therapy on DC function, including their ability to promote T cell–mediated antitumor immunity.

Sunitinib Versus Sorafenib: Similar Results?

If sunitinib can effectively serve as an immunomodulator, is it fair to extrapolate the findings to sorafenib? Sorafenib is also a multikinase inhibitor initially developed to inhibit the Raf1-kinase pathway. Until a study by Hipp and colleagues[18] appeared, the effects of sorafenib and sunitinib on the development and function of normal nonmalignant hematopoetic cells had not been evaluated. The results suggest that sorafenib, but not sunitinib, has a negative effect on DC phenotype and inhibits cytokine secretion, migration ability, and T-cell stimulatory capacity. The phenotype of T cells was not affected.

When the 2 agents were compared in a mouse model, differences emerged between them with respect to primary immune responses stimulation. To analyze the effects of both TKIs on cytotoxic T-cell induction in vivo, mice were pretreated with sorafenib or sunitinib and immunized with OVA257-264 peptide. Sorafenib treatment reduced the induction of antigen-specific T cells but sunitinib did not. The number of regulatory T cells was reduced in peripheral blood mononuclear cells from mice treated with sunitinib but not sorafenib. Thus, sorafenib was able to interfere with DC function by reducing the ability of DC to respond to inflammatory signals, by impairing DC migration and their ability to activate T cells. Because sunitinib had no effects on DC maturation and function and did not alter priming of T-cells to antigen in vivo, the researchers concluded that sunitinib may be a good candidate for combination therapy with vaccines or adoptive T cell therapy.

Defining the Mechanisms by Which Sunitinib Modulates Immune Cells

Much remains to be explained about how sunitinib can reduce regulatory cell numbers (MDSC and Treg) and restore T cell responses. There is the possibility that sunitinib has a direct effect on host immune cells or MDSC that occurs independently of the drug's antivasculature effect. Indeed, our current evidence suggests that sunitinib can directly act on MDSC. We found that culturing isolated MDSC with sunitinib for 48 hours induced apoptosis and this effect was selective because T cell viability was not impaired.[13]

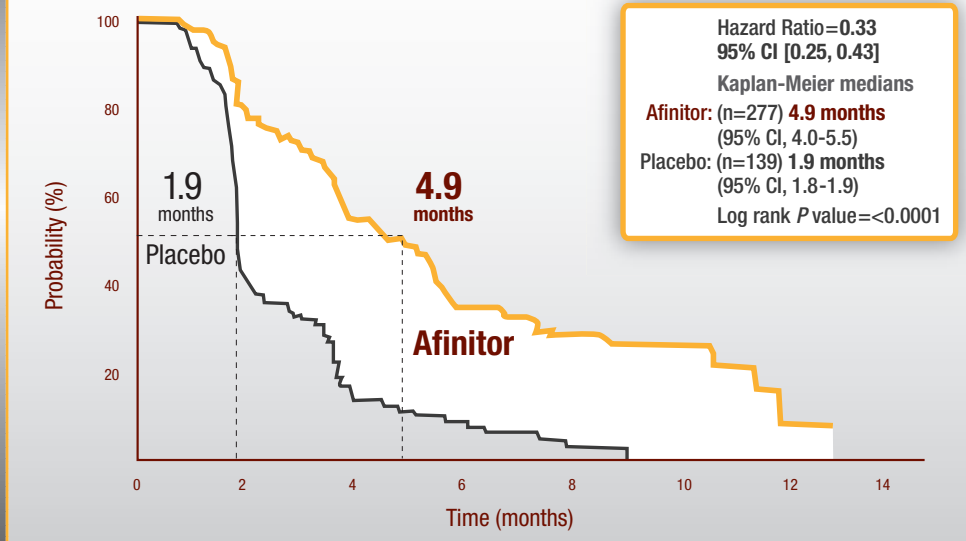
Sunitinib is known to target multiple receptors tyrosine kinases including vascular endothelial growth factor receptor (VEGFR)1 and 2, c-kit, platelet-derived growth factor receptor (PDGFR), and Flt3. Some of these receptors are expressed, to varying degrees, on MDSC including VEGFR1 and VEGFR2 and Flt3 (George S et al, unpublished data).[19] However, which RTK or combina-

(continued on page 31)

In advanced RCC:

Afinitor doubled median PFS after progression on sunitinib*[1]

Progression-free survival (PFS) after progression on sunitinib or sorafenib[1]



- 4.9 months median PFS with Afinitor + BSC† (vs 1.9 months with placebo + BSC; *P*<0.0001)[1]
- HR 0.33=67% reduction in risk of progression
- Effective for patients with all prognostic scores[1]

For more information about Afinitor, call 1-888-4Afinitor (1-888-423-4648) or visit www.AFINITOR.com
For reimbursement questions, call 1-888-5AfiniTRAC (1-888-523-4648).

*In the RECORD-1 trial, Afinitor extended PFS after progression on sunitinib or sorafenib.[1,2]
†BSC=best supportive care.

Important Safety Information

There have been reports of non-infectious pneumonitis and infections, some with fatal outcomes. Oral ulceration has been reported. Elevations of serum creatinine, glucose, lipids, and triglycerides and reductions of hemoglobin, lymphocytes, neutrophils, and platelets have been reported.

Please see Important Safety Information on right side of page.
Please see Brief Summary of full Prescribing Information on the following pages.

Afinitor is indicated for the treatment of patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib.

Important Safety Information

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

Non-infectious pneumonitis is a class effect of rapamycin derivatives, including Afinitor. Fatal outcomes have been observed. If symptoms are moderate or severe, patients should be managed with dose interruption until symptoms improve or discontinuation, respectively. Corticosteroids may be indicated. Afinitor may be reintroduced at 5 mg daily depending on the individual clinical circumstances.

Afinitor has immunosuppressive properties and may predispose patients to bacterial, fungal, viral or protozoan infections, including infections with opportunistic pathogens. Localized and systemic infections, including pneumonia, other bacterial infections, invasive fungal infections, and viral infections including reactivation of hepatitis B virus have occurred. Some of these infections have been severe (e.g. leading to respiratory or hepatic failure) or fatal. Complete treatment of pre-existing invasive fungal infections prior to starting treatment. While taking Afinitor be vigilant for signs and symptoms of infection; if a diagnosis of infection is made, institute appropriate treatment promptly and consider interruption or discontinuation of Afinitor. If a diagnosis of invasive systemic fungal infection is made, discontinue Afinitor and treat with appropriate antifungal therapy.

Oral ulcerations (i.e. mouth ulcers, stomatitis, and oral mucositis) have occurred in patients treated with Afinitor. In such cases, topical treatments are recommended, but alcohol- or peroxide-containing mouthwashes should be avoided. Antifungal agents should not be used unless fungal infection has been diagnosed.

Elevations of serum creatinine, glucose, lipids, and triglycerides and reductions of hemoglobin, lymphocytes, neutrophils, and platelets have been reported in clinical trials. Renal function, hematological parameters, blood glucose, and lipids should be evaluated prior to treatment and periodically thereafter. When possible, optimal glucose and lipid control should be achieved before starting a patient on Afinitor.

Avoid concomitant use with strong CYP3A4 or PgP inhibitors. If co-administration with moderate CYP3A4 or PgP inhibitors is required, use caution and reduce dose of Afinitor to 2.5 mg daily. Increase the Afinitor dose if co-administered with a strong CYP3A4 inducer.

Afinitor should not be used in patients with severe hepatic impairment. Afinitor dose should be reduced to 5 mg daily for patients with moderate hepatic impairment.

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

Fetal harm can occur if Afinitor is administered to a pregnant woman.

The most common adverse reactions (incidence ≥30%) were stomatitis (44%), infections (37%), asthenia (33%), fatigue (31%), cough (30%), and diarrhea (30%). The most common grade 3/4 adverse reactions (incidence ≥3%) were infections (9%), dyspnea (8%), fatigue (5%), stomatitis (4%), dehydration (4%), pneumonitis (4%), abdominal pain (3%), and asthenia (3%). The most common laboratory abnormalities (incidence ≥50%) were anemia (92%), hypercholesterolemia (77%), hypertriglyceridemia (73%), hyperglycemia (57%), lymphopenia (51%), and increased creatinine (50%). The most common grade 3/4 laboratory abnormalities (incidence ≥3%) were lymphopenia (18%), hyperglycemia (16%), anemia (13%), hypophosphatemia (6%), and hypercholesterolemia (4%). Deaths due to acute respiratory failure (0.7%), infection (0.7%), and acute renal failure (0.4%) were observed on the Afinitor arm.

References: 1. Afinitor [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2010. **2.** Motzer RJ, Escudier B, Oudard S, et al; for the RECORD-1 Study Group. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. *Lancet.* 2008;372:449-456.

NOVARTIS ONCOLOGY

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

Change tracks

Novartis Pharmaceuticals Corporation
East Hanover, NJ 07936

Printed in U.S.A. 08/10 C-AFI-100065

AFINITOR *(everolimus)* tablets for oral administration

Initial U.S. Approval: 2009

BRIEF SUMMARY: Please see package insert for full prescribing information.

1 INDICATIONS AND USAGE

AFINITOR® is indicated for the treatment of patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib.

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Non-infectious Pneumonitis

Non-infectious pneumonitis is a class effect of rapamycin derivatives, including AFINITOR. In the randomized study, non-infectious pneumonitis was reported in 14% of patients treated with AFINITOR. The incidence of Common Toxicity Criteria (CTC) grade 3 and 4 non-infectious pneumonitis was 4% and 0%, respectively *[see Adverse Reactions (6.1)]*. Fatal outcomes have been observed.

Consider a diagnosis of non-infectious pneumonitis in patients presenting with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough, or dyspnea, and in whom infectious, neoplastic, and other causes have been excluded by means of appropriate investigations. Advise patients to report promptly any new or worsening respiratory symptoms.

Patients who develop radiological changes suggestive of non-infectious pneumonitis and have few or no symptoms may continue AFINITOR therapy without dose alteration. If symptoms are moderate, consider interrupting therapy until symptoms improve. The use of corticosteroids may be indicated. AFINITOR may be reintroduced at 5 mg daily.

For cases where symptoms of non-infectious pneumonitis are severe, discontinue AFINITOR therapy and the use of corticosteroids may be indicated until clinical symptoms resolve. Therapy with AFINITOR may be re-initiated at a reduced dose of 5 mg daily depending on the individual clinical circumstances.

5.2 Infections

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

5.3 Oral Ulceration

Mouth ulcers, stomatitis, and oral mucositis have occurred in patients treated with AFINITOR. In the randomized study, approximately 44% of AFINITOR-treated patients developed mouth ulcers, stomatitis, or oral mucositis, which were mostly CTC grade 1 and 2 *[see Adverse Reactions (6.1)]*. In such cases, topical treatments are recommended, but alcohol- or peroxide-containing mouthwashes should be avoided as they may exacerbate the condition. Antifungal agents should not be used unless fungal infection has been diagnosed *[see Drug Interactions (7.1)]*.

5.4 Laboratory Tests and Monitoring

Renal Function

Elevations of serum creatinine, usually mild, have been reported in clinical trials *[see Adverse Reactions (6.1)]*. Monitoring of renal function, including measurement of blood urea nitrogen (BUN) or serum creatinine, is recommended prior to the start of AFINITOR therapy and periodically thereafter.

Blood Glucose and Lipids

Hyperglycemia, hyperlipidemia, and hypertriglyceridemia have been reported in clinical trials *[see Adverse Reactions (6.1)]*. Monitoring of fasting serum glucose and lipid profile is recommended prior to the start of AFINITOR therapy and periodically thereafter. When possible, optimal glucose and lipid control should be achieved before starting a patient on AFINITOR.

Hematological Parameters

Decreased hemoglobin, lymphocytes, neutrophils, and platelets have been reported in clinical trials *[see Adverse Reactions (6.1)]*. Monitoring of complete blood count is recommended prior to the start of AFINITOR therapy and periodically thereafter.

5.5 Drug-drug Interactions

Due to significant increases in exposure of everolimus, co-administration with strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) or P-glycoprotein (PgP) should be avoided. Grapefruit, grapefruit juice and other foods that are known to affect cytochrome P450 and PgP activity should also be avoided during treatment *[see Dosage and Administration (2.2) in the full prescribing information and Drug Interactions (7.1)]*.

A reduction of the AFINITOR dose is recommended when co-administered with a moderate CYP3A4 inhibitor (e.g., amprenavir, fosamprenavir, aprepitant, erythromycin, fluconazole, verapamil, diltiazem) or PgP inhibitor *[see Dosage and Administration (2.2) in the full prescribing information and Drug Interactions (7.1)]*.

An increase in the AFINITOR dose is recommended when co-administered with a strong CYP3A4 inducer (e.g., St. John's Wort (Hypericum perforatum), dexamethasone, prednisone, prednisolone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) *[see Dosage and Administration (2.2) in the full prescribing information and Drug Interactions (7.2)]*.

5.6 Hepatic Impairment

The safety and pharmacokinetics of AFINITOR were evaluated in a study in eight patients with moderate hepatic impairment (Child-Pugh class B) and eight subjects with normal hepatic function. Exposure was increased in patients with moderate hepatic impairment, therefore a dose reduction is recommended.

AFINITOR has not been studied in patients with severe hepatic impairment (Child-Pugh class C) and should not be used in this population *[see Dosage and Administration (2.2) in the full prescribing information and Use in Specific Populations (8.7)]*.

5.7 Vaccinations

The use of live vaccines and close contact with those who have received live vaccines should be avoided during treatment with AFINITOR. Examples of live vaccines are: intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines.

5.8 Use in Pregnancy

Pregnancy Category D

There are no adequate and well-controlled studies of AFINITOR in pregnant women. However, based on mechanism of action, AFINITOR may cause fetal harm when administered to a pregnant woman. Everolimus caused embryo-fetal toxicities in animals at maternal exposures that were lower than human exposures at the recommended dose of 10 mg daily. If this drug is used during pregnancy or if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to use an effective method of contraception while using AFINITOR and for up to 8 weeks after ending treatment *[see Use in Specific Populations (8.1)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in another section of the label:

- Non-infectious pneumonitis *[see Warnings and Precautions (5.1)]*.
- Infections *[see Warnings and Precautions (5.2)]*.

6.1 Clinical Studies Experience

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

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

The most common adverse reactions (incidence ≥30%) were stomatitis, infections, asthenia, fatigue, cough, and diarrhea. The most common grade 3/4 adverse reactions (incidence ≥3%) were infections, dyspnea, fatigue, stomatitis, dehydration, pneumonitis, abdominal pain, and asthenia. The most common laboratory abnormalities (incidence ≥50%) were anemia,

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

Table 1 compares the incidence of treatment-emergent adverse reactions reported with an incidence of ≥10% for patients receiving AFINITOR 10 mg daily versus placebo. Within each MedDRA system organ class, the adverse reactions are presented in order of decreasing frequency.

Table 1
Adverse Reactions Reported in at least 10% of Patients and at a Higher Rate in the AFINITOR Arm than in the Placebo Arm

	AFINITOR 10 mg/day N=274			Placebo N=137		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Any Adverse Reaction	**97**	**52**	**13**	**93**	**23**	**5**
Gastrointestinal Disorders						
Stomatitis[a]	44	4	<1	8	0	0
Diarrhea	30	1	0	7	0	0
Nausea	26	1	0	19	0	0
Vomiting	20	2	0	12	0	0
Infections and Infestations[b]	37	7	3	18	1	0
General Disorders and Administration Site Conditions						
Asthenia	33	3	<1	23	4	0
Fatigue	31	5	0	27	3	<1
Edema peripheral	25	<1	0	8	<1	0
Pyrexia	20	<1	0	9	0	0
Mucosal inflammation	19	1	0	1	0	0
Respiratory, Thoracic and Mediastinal Disorders						
Cough	30	<1	0	16	0	0
Dyspnea	24	6	1	15	3	0
Epistaxis	18	0	0	0	0	0
Pneumonitis[c]	14	4	0	0	0	0
Skin and Subcutaneous Tissue Disorders						
Rash	29	1	0	7	0	0
Pruritus	14	<1	0	7	0	0
Dry skin	13	<1	0	5	0	0
Metabolism and Nutrition Disorders						
Anorexia	25	1	0	14	<1	0
Nervous System Disorders						
Headache	19	<1	<1	9	<1	0
Dysgeusia	10	0	0	2	0	0
Musculoskeletal and Connective Tissue Disorders						
Pain in extremity	10	1	0	7	0	0
Median Duration of Treatment (d)	**141**			**60**		

CTCAE Version 3.0
[a]Stomatitis (including aphthous stomatitis), and mouth and tongue ulceration.
[b]Includes all preferred terms within the 'infections and infestations' system organ class, the most common being nasopharyngitis (6%), pneumonia (6%), urinary tract infection (5%), bronchitis (4%), and sinusitis (3%), and also including aspergillosis (<1%), candidiasis (<1%), and sepsis (<1%).
[c]Includes pneumonitis, interstitial lung disease, lung infiltration, pulmonary alveolar hemorrhage, pulmonary toxicity, and alveolitis.

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

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

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

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

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

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

Psychiatric disorders: Insomnia (9%)

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

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

Vascular disorders: Hypertension (4%)

Renal and urinary disorders: Renal failure (3%)

Cardiac disorders: Tachycardia (3%), congestive cardiac failure (1%)

Musculoskeletal and connective tissue disorders: Jaw pain (3%)

Hematologic disorders: Hemorrhage (3%)

Key treatment-emergent laboratory abnormalities are presented in Table 2.

Table 2
Key Laboratory Abnormalities Reported at a Higher Rate in the AFINITOR Arm than the Placebo Arm

Laboratory Parameter	AFINITOR 10 mg/day N=274			Placebo N=137		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Hematology[a]						
Hemoglobin decreased	92	12	1	79	5	<1
Lymphocytes decreased	51	16	2	28	5	0
Platelets decreased	23	1	0	2	0	<1
Neutrophils decreased	14	0	<1	4	0	0
Clinical Chemistry						
Cholesterol increased	77	4	0	35	0	0
Triglycerides increased	73	<1	0	34	0	0
Glucose increased	57	15	<1	25	1	0
Creatinine increased	50	1	0	34	0	0
Phosphate decreased	37	6	0	8	0	0
Aspartate transaminase (AST) increased	25	<1	<1	7	0	0
Alanine transaminase (ALT) increased	21	1	0	4	0	0
Bilirubin increased	3	<1	<1	2	0	0

CTCAE Version 3.0
[a]Includes reports of anemia, leukopenia, lymphopenia, neutropenia, pancytopenia, thrombocytopenia.

Information from further clinical trials
In clinical trials, everolimus has been associated with serious cases of hepatitis B reactivation, including fatal outcomes.

7 DRUG INTERACTIONS

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

7.1 Agents that may Increase Everolimus Blood Concentrations

CYP3A4 Inhibitors and PgP Inhibitors: In healthy subjects, compared to AFINITOR treatment alone there were significant increases in everolimus exposure when AFINITOR was coadministered with:

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

Concomitant strong inhibitors of CYP3A4 and PgP should not be used *[see Warnings and Precautions (5.5)]*.

Use caution when AFINITOR is used in combination with moderate CYP3A4 or PgP inhibitors. If alternative treatment cannot be administered reduce the AFINITOR dose. *[See Dosage and Administration (2.2) in the full prescribing information]*

7.2 Agents that may Decrease Everolimus Blood Concentrations

CYP3A4 Inducers: In healthy subjects, co-administration of AFINITOR with rifampin, a strong inducer of CYP3A4, decreased everolimus AUC and C_{max} by 64% and 58% respectively, compared to everolimus treatment alone. Consider a dose increase of AFINITOR when co-administered with

strong inducers of CYP3A4 (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital) or PgP if alternative treatment cannot be administered. St. John's Wort may decrease everolimus exposure unpredictably and should be avoided *[see Dosage and Administration (2.2) in the full prescribing information]*.

7.3 Agents whose Plasma Concentrations may be Altered by Everolimus

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D *[see Warnings and Precautions (5.8)]*

There are no adequate and well-controlled studies of AFINITOR in pregnant women. However, based on mechanism of action, AFINITOR may cause fetal harm when administered to a pregnant woman. Everolimus caused embryo-fetal toxicities in animals at maternal exposures that were lower than human exposures at the recommended dose of 10 mg daily. If this drug is used during pregnancy or if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to use an effective method of contraception while receiving AFINITOR and for up to 8 weeks after ending treatment.

In animal reproductive studies, oral administration of everolimus to female rats before mating and through organogenesis induced embryo-fetal toxicities, including increased resorption, pre-implantation and post-implantation loss, decreased numbers of live fetuses, malformation (e.g., sternal cleft) and retarded skeletal development. These effects occurred in the absence of maternal toxicities. Embryo-fetal toxicities occurred at approximately 4% the exposure ($AUC_{0\text{-}24h}$) in patients receiving the recommended dose of 10 mg daily. In rabbits, embryotoxicity evident as an increase in resorptions occurred at an oral dose approximately 1.6 times the recommended human dose on a body surface area basis. The effect in rabbits occurred in the presence of maternal toxicities.

In a pre- and post-natal development study in rats, animals were dosed from implantation through lactation. At approximately 10% of the recommended human dose based on body surface area, there were no adverse effects on delivery and lactation and there were no signs of maternal toxicity. However, there was reduced body weight (up to 9% reduction from the control) and slight reduction in survival in offspring (~5% died or missing). There were no drug-related effects on the developmental parameters (morphological development, motor activity, learning, or fertility assessment) in the offspring.

Doses that resulted in embryo-fetal toxicities in rats and rabbits were ≥0.1 mg/kg (0.6 mg/m^2) and 0.8 mg/kg (9.6 mg/m^2), respectively. The dose in the pre- and post-natal development study in rats that caused reduction in body weights and survival of offspring was 0.1 mg/kg (0.6 mg/m^2).

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

8.5 Geriatric Use

In the randomized study, 41% of AFINITOR-treated patients were ≥65 years in age, while 7% percent were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

No dosage adjustment is required in elderly patients *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

8.6 Renal Impairment

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

8.7 Hepatic Impairment

For patients with moderate hepatic impairment (Child-Pugh class B), the dose should be reduced to 5 mg daily *[see Dosage and Administration (2.2) in the full prescribing information, Warnings and Precautions (5.6) and Clinical Pharmacology (12.3) in the full prescribing information]*.

The impact of severe hepatic impairment (Child-Pugh class C) has not been assessed and use in this patient population is not recommended *[see Warnings and Precautions (5.6)]*.

10 OVERDOSAGE

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

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

16 STORAGE

Store AFINITOR (everolimus) tablets at 25°C (77°F); excursions permitted between 15°-30°C (59°-86°F). [See USP Controlled Room Temperature.] Store in the original container, protect from light and moisture. Keep this and all drugs out of the reach of children.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.

AFINITOR tablets should not be crushed. Do not take tablets which are crushed or broken.

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(continued from page 25)

tion of RTKs expressed by MDSC are the targets of sunitinib-mediated reduction in MDSC is not well defined. A study by Ozao-Choy and colleagues[10] demonstrated that c-kit may be one target since c-kit mutant mice bearing MCA26 tumor had significantly less intratumor MDSC compared with wild-type tumor. Moreover, sunitinib treatment did not further reduce MDSC numbers in the c-kit mutant mice when compared with the dramatic reduction in MDSC from wild-type tumor bearing mice. Our preliminary data suggest that sunitinib was more effective than other TKI inhibitors (imatinib or vatalanib,) in reducing splenic MDSC levels in tumor bearing mice (Cohen et al, unpublished data). Thus, additional studies are needed to identify which TKI receptors expressed on MDSC are important for sunitinib-mediated reduction in MDSC.

It is less likely that sunitinib works to reduce MDSC numbers by blocking the production of tumor-produced growth factors implicated in the buildup of MSDC (G-CSF, VEGF, SCF) because it is known that sunitinib does not reduce their production but can actually increase their plasma levels.[20]

Sunitinib has recently been shown to block activation of the transcription factor STAT3, (signal transducer and activator of transcription3). Persistent activation of STAT3 in tumor cells promotes their survival, angiogenic activity, and proliferation.[21] STAT3 is activated in most cancer cell types, including RCC.[11,22] STAT3 activation is downstream of different cytokine receptors (eg, IL6), and growth factor receptors, when stimulated by their respective ligands induce a number of genes important in promoting inflammation and cancer progression.[23] The activation of cytokines and growth factors in a STAT3-dependent manner by tumors in turn activates STAT3 in various immune cell types and leads to immune suppression within the tumor microenvironment. The constitutive activation of STAT3 in immune regulatory cells such as Tregs and macrophages results in the suppression of a Th-1 type immune response.[11,21] STAT3 activation is also involved in tumor accumulation of MDSCs via a mechanism that is partly dependent on the up-regulation of S100A9 and S100A8 proteins in myeloid precursors.[22] The negative impact of STAT3 activation on immune responses can be reversed by ablating STAT3, which results in reduction in regulatory cells, improved DC function, and $CD8^+$ T-cell activation.[23,24]

In a RCC mouse model, Xin and colleagues[11] showed that sunitinib treatment reduced tumor size, which coincided with a substantial reduction in tumor expression of activated STAT3 (p-STAT3) along with a reduction in protein-associated tumor cell proliferation and survival (cyclin D, cyclin E and survivin). Sunitinib inhibited STAT3 activity in tumor cells and perhaps also in tumor endothelial cells, a prime target of sunitinib. In addition, tumor cell apoptosis occurred before tumor vasculature collapse, which suggests that tumor cell apoptosis was an independent factor that affects RCC response to sunitinib. The findings from Xin and colleagues further suggest a rationale for the efficacy of sunitinib as an immunomodulator in patients with RCC.

Immunomodulation may be mediated by STAT3 inhibition.[11] Indeed they showed that sunitinib treatment inhibited STAT3 activity in MDSC and macrophages infiltrating the tumor, which coincided with a reduction in expression of several STAT3-regulated angiogenic genes. This reduction in STAT3 likely contributed to the reduction in MDSC and Treg cells. Further study is needed to determine whether STAT3 is a biomarker for sunitinib response and resistance in RCC. Another issue raised by the researchers and relevant for future study is the potential value of combination therapies with sunitinib and immunotherapy.

Other studies highlight the role of STAT3 as a contributing factor in tumor angiogenesis and metastasis.[11] STAT3 activity, for example, can promote endothelial migration and potentiates a tumor's ability to form capillary tubes. If STAT3 activity is inhibited, for example by sunitinib, then endothelial migration and formation of capillary tubes may be limited in vitro and in vivo.

Potential of MDSC to Promote Resistance

It appears that most patients who receive sunitinib monothearpy will, over time, become resistant, although the responsible mechanism(s) are not well defined. One possible contributing mechanism may involve MDSC that persist after sunitinib treatment and promote proangiogenic activity.[14,25] MDSC are not only important in mediating T cell suppression observed in the tumor bearing host, they also promote tumor growth by enhancing angiogenesis. Indeed co-injection of murine tumors with MDSC ($Gr1^+CD11b^+$) increased vascular density in the tumor, reduced necrosis and augmented tumor growth.[26,27] MDSC also produce high levels of matrix metallopeptidase 9 (MMP9), which can function as an angiogenic switch during tumorigenesis. Moreover, MDSC from MMP9 knockout mice have a significant reduction in their tumor promoting activity.[27]

Additional studies suggest that MDSC represent a mechanism of resistance to anti-VEGF treatment in mouse tumor models.[28,29] We reported that the 4T1 mammary tumor model was resistant to sunitinib based on minimal reduction in tumor growth, which was associated with the persistence of MDSC in the tumor even though sunitinib reduced MDSC levels in the spleen. This persistence of MDSC in the 4T1 tumor was attributable to local production of growth factors such as granulocyte macrophage colony-stimulation factor (GM-CSF) that protected MDSC, via a STAT5-dependent pathway, from sunitinib-induced apoptosis and inhibition of proliferation.[14] Results from a current study in RCC patients who receive sunitinib in a neoadjuvant setting show that some patients have persistent levels of MDSC with a diminished T cell response, thus mimick-

ing the findings in the 4T1 mouse model.[25] Further studies are needed to assess whether MDSC promote resistance to sunitinib via a STAT5 and GM-CSF dependent pathway.

Rationale for Combining Sunitinib With Immunotherapy in Cancer Patients

Although the efficacy of sunitinib has changed the first- and second-line treatment for this disease, patients with RCC, eventually have tumor progression after initial tumor regression upon VEGFR-interfering therapy. Thus there is growing interest in regimens that combine immunotherapy with agents that interfere with VEGFR signaling. The observation that sunitinib treatment, at least in part, normalizes disturbed myeloid differentiation pathways and results in a potentially more favorable immunocompetent state, certainly supports this notion.[13,15] A sustained reduction in abnormally high numbers of potentially immunosuppressive MDSC, combined with increased rates of otherwise down-regulated immunostimulatory MDC-1, for up to at least 2 weeks after the 4 weeks of sunitinib administration, may provide a window, in which patients are particularly amenable to immunotherapeutic approaches.

If the tumor microenvironment can be manipulated in these ways, the obvious question concerns the extent to which such strategies might be effective when combined with immune-based cancer therapies to improve survival. At this point, no study has shown a survival advantage of such an approach in humans but data from 3 studies in different mouse tumor models suggest that it may be possible (**Table**).

A study by Ozao-Choy[10] demonstrated in a colon cancer mouse model (MCA26) that sunitinib treatment enhanced the antitumor activity of IL-12 expressed in an adenoviral vector when combined with 41BBLigand, a costimulatory molecule known to enhance T cell activation. Sunitinib significantly improved the long-term survival rate of tumor bearing mice treated with IL12/41BB immunotherapy. Treatment with sunitinib decreased the number of MDSC and Treg in advanced tumor-bearing animals. Furthermore, it not only reduced the suppressive function of MDSCs but also prevented tumor-specific T-cell anergy and Treg development.

These findings opened an avenue of investigation only recently explored: that sunitinib modulates the tumor microenvironment not only by decreasing Treg and MDSC numbers in the tumor but also by down-regulating cytokines, such as IIL-10 and TGF-β, and important immune suppressive costimulatory receptors, such as PD-1 and CTLA. Sunitinib treatment can also increase the percentage of CD8+ T cells and enhance IFNγ gene expression in the tumor. A limited number of patient blood samples showing similar results, suggested that 1 week of sunitinib treatment in patients with metastatic cancer may substantially affect the composition of immune cells in the peripheral blood; however, these results should be viewed as preliminary.

A second study demonstrated that sunitinib, when given in combination with a DC-based vaccine to mice bearing B16-OVA (M05) tumors, generated animals with regressing tumors (tumor free >60 days posttreatment) compared with no regressing tumors in mice who received either vaccine or sunitinib alone.[30] The timing of sunitinib treatment relative to DC vaccine was important and showed that superior efficacy was noted when sunitinb was initiated at the time of primary or secondary vaccination.

The effect that combination therapy versus monotherapy had on immune cells and chemokines expression was examined. The most dramatic reduction in Tregs, MDSC, and immunosuppressive molecules expressed by MDSC (arginase-1, IDO, iNOS) was observed in the tumors of mice treated with the combination. Likewise, the combination treatment was most effective at prolonging an augmented type-1 anti-OVA $CD8^+$ T cell response. The trafficking of type-1 T cell to tumor was dependent on sunitinib/vaccine induced expression of VCAM-1 and CXCR3 ligand chemokines on vascular cells within the tumor. This study highlights the importance of combination therapy in stimulating a robust antitumor T cell response in mice with established tumors.

A third study showed that adoptive T cell therapy in mouse tumor models (B16 OVA and Renca) could be significantly improved by combining T cell transfer with sunitinib to reduce expression of activated STAT3 in adoptively transferred lymphocytes, which diminishes the therapeutic activity of these cells.[12] The results of this study showed that tumor conditioned media induced STAT3 in $CD8^+$ T cells that was blocked by sunitinib treatment. Moreover, it was shown that $CD8^+$ T cells genetically deficient in STAT3, when transferred into mice bearing B16-OVA, were able to survive, expand, and reduce tumor growth. They also showed that when sunitinib was combined with adoptive transfer of $CD8^+$ T cells into Renca (or B16-OVA) bearing mice, greater tumor reduction was observed than with either T cells or sunitinib treatment alone. In addition, sunitinib inhibited STAT3 activation in DC and T cells and blocked the induction of Treg cells from the Foxp3- T cell population. The data from this study suggest that silencing STAT3 in adoptively transferred T cells either by engineering STAT3-/- T cells or by using sunitinib will improve the efficacy of T cell therapy.

It remains to be seen how much translational impact these studies will have on clinical practice, but if the animal models can be further explored and extrapolated to a human population, perhaps targeted TKIs can be used in a novel synergistic way to enhance the efficacy of existing immune-based therapies for metastatic cancer patients.

The translation of sunitinib combined with immunotherapy from animal studies to human clinical trials has begun. Argos Therapeutics conducted a phase 2 trial in previously untreated patients with advanced stage RCC who received sunitinib combined with mature DC co-

Table. Sunitinib Combined With Immunotherapy in Murine Tumor Models

Therapy and outcome	Ozao-Choy[10]	Bose[30]	Kujawski[12]
4-1BBLigand/IL12(adenoviral vector)/sunitinib (MCA26)	X		
OVA-DC vaccine /sunitinib (B16-OVA)		X	
CD8+T cells/sunitinib(Renca)			X
Synergistic reduction in tumor volume	X	X	X
Increase in number of tumor free mice post treatment with combination therapy	X	X	
Reversing immune suppression			
MDSC reduction peripherally and in tumor	X	X	
Treg reduction	X	X	X
Reduction in tumor-induced Treg conversion	X		X
Reduced expression of immunosuppressive cytokines and co-stimulatory molecules on tumor infiltrating lymphocytes IL10, PD1, PDL-1 and CTLA4 IL10 Reduced expression of known chemo-attractants for MDSC and Tregs; CXCL12/SDF-1 , CCL2/CPM-1, CXCL5/ENA-78, S100A8, and S100A9		X	
Reduced expression of MDSC-associated products; arginase 1, IDO, and iNOS		X	
Promotion of anti-tumor immune response			
Improved mature DC numbers		X	
Prevention of T cell anergy	X		
Increased expression of type-1 associated transcripts CXCR3 and CXCR3 ligands, CXCL9/Mig, CXCL10/IP10, CXCL11/I-TAC		X	
Induced anti-Ova CD8+ T cell response		X	X
Increased production of IFN and increased frequency of OVA-specific CD8+ T cells (tetramer+) X Table 1: Sunitinib Combined with Immunotherapy in Murine Tumor Models		X	

electroporated with CD40LIVT RNA and autologous total tumor RNA as a source of antigen for stimulating an antitumor immune response (ASCO 2010). Patients received 4 weeks of sunitinib treatment followed by a 2-week rest period before receiving 5 intradermal injections of antigen loaded DC every 3 weeks along with sunitinib, every 3 months until disease progression or end of study (clinicaltrials.gov).

The combination was well tolerated and interim assessment suggests positive median progression-free survival (PFS) results (14 months for intermediate risk patients and 6 months for the risk group). This study is ongoing but not recruiting patients and no data have been presented on changes in patients immune suppression or immune enhancement status. A phase 3 trial is planned.

The German based company, Immatics Biotechnologie is conducting a multicenter, open label, randomized phase 3 trial that is open for enrollment. This study will test whether their multipeptide cancer vaccine (IMA901) will prolong overall survival in patients with mRCC when combined with sunitinib. IMA901 consist of 10 tumor-associated peptides that are overexpressed on a high percentage of RCC. In their phase 2 trial, patients who developed a vaccine induced response to peptides in IMA901 displayed longer survival compared with those without a response (ASCO 2010). It is hoped that these initial trials will not only provide data on efficacy but also on how sunitinib can modulate immune cells in patients with RCC.

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Is Renal Cell Carcinoma Really Radioresistant? Experience With Stereotactic Body Radiotherapy in Patients for Primary and Metastatic Renal Cell Carcinoma

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Renal cell carcinoma (RCC) has been traditionally considered radioresistant. Radioresistance may have implications both in the laboratory and the clinic. Clinically, it typically refers to tumors poorly controlled with conventionally attainable radiotherapy schedules. In the lab, it more precisely refers to characteristics of the clonogenic survival curve. Survival curves have been measured for many human cell lines in culture. They describe the ability of cells to maintain the functional machinery to form colonies on growth media (in vitro) after variable doses of radiation exposure. The classic measure of radiosensitivity is the surviving fraction after 2 Gy exposure (SF_{2Gy}), which was chosen because it is the conventional daily dose exposure used in radiation oncology clinics. In the case of RCC, tumor cells appear to be radioresistant to this 2 Gy exposure by both clinical (poor tumor control) and laboratory (high SF_{2Gy}) criteria.

Ning and colleagues[1] at Stanford University performed clonogenic survival assays with 2 human RCC cell lines: Caki-1 and A498. The cells were irradiated with 0 to 15 Gy and surviving fractions were calculated. Survival curves of both cell lines exhibited a small decrease in survival from 0 to 6 Gy (called the "shoulder" region) followed by an exponential decrease in survival at radiation doses above 6 Gy. As shown in **Figure 1**, while cell survival for RCC is only modestly effected at 2 Gy (ie, the cells are radioresistant at 2 Gy), the effect of radiation is fairly profound at doses over 6 Gy.

In the linear quadratic mathematical representation of the survival curve, there are 2 components of cell survival: one is proportional to the dose (α) and the other is proportional to the square of the dose (β) . As such, this α component contributes a proportionally larger effect on decreasing cell survival in the lower dose range, ie, at the 2 Gy conventional dose range. The dose at which both components of cell killing are equal is known as the α/β ratio. Generally, cell lines with a high α/β ratio (≥ 10) are considered radiosensitive, again mostly related to more effective killing in the low-dose range. In the above study, the α/β ratio for the Caki-1 cell line was 6.9 versus 2.6 for the A498 cell line, which indicates radioresistance. RCC has a broad shoulder to the survival curve and relates biologically to more effective repair of radiation injury, at least in the lower dose range.

Ultimately, cell death occurs by a variety of mechanisms. Tumor cells with a high level of radiation-induced apoptosis (programmed cell death) tend to be relatively sensitive to radiation, whereas tumor cells with a low level of radiation-induced apoptosis are relatively resistant to radiation.[2]

Conventionally fractionated radiotherapy is rarely used to treat primary renal tumors. Limited radiation tolerance of the normal kidneys and the surrounding tissues along with the feeling that the tumor is radioresis-

Keywords: Stereotactic body radiotherapy, renal cell carcinoma, radioresistance

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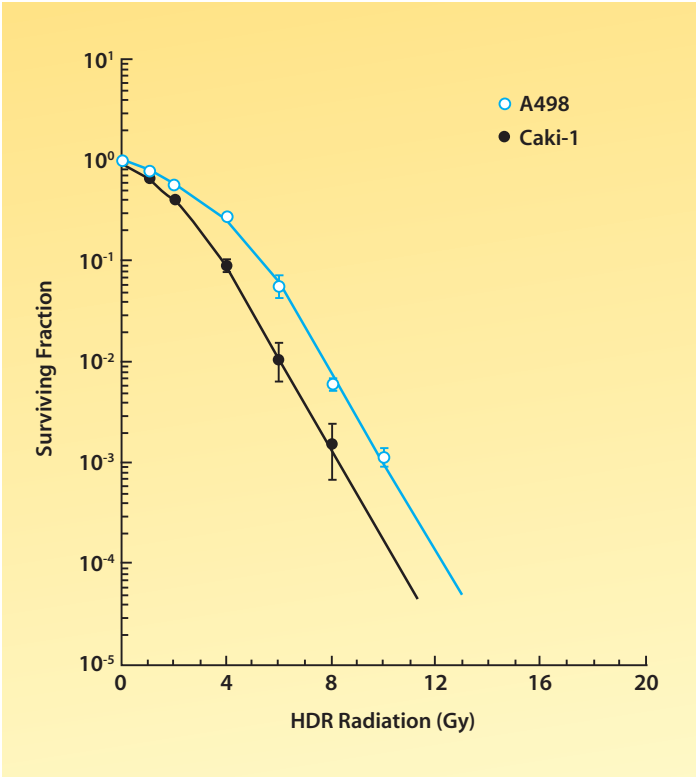

Figure 1. Survival curves for 2 human renal cell carcinoma lines, Caki-1 and A498, are shown. Cells were irradiated at a dose rate of 430 cGy per minute using a cesium-137 irradiator, and an in vitro clonogenic assay was performed. The surviving fraction is shown as a function of dose. Data points represent the mean ± standard deviation. The survival curves are fitted by the linear-quadratic model. Tumors with radiation survival curves characterized by a steep initial slope and small shoulder tend to be relatively more sensitive to radiation than tumors with a flat initial slope and large shoulder. Reproduced with permission from Ning et al.[1]

tant, have prevented routine use of radiotherapy for kidney tumors. The advent of the image guided stereotactic body radiotherapy (SBRT) system has made feasible what was once technically prohibitive. Stereotactic body radiotherapy has been used successfully to treat tumors at various anatomic sites including the lung and liver.[3-14] Stereotactic body radiotherapy involves tightly conforming high dose per fraction of therapeutic radiation confined to a small region of the body with the goal of ablating the target tumor and sparing surrounding normal tissues. This is accomplished by utilizing multiple beams to converge on the target from various directions. In addition, the system must allow monitoring of the target via tracking implanted fiducial markers or direct imaging of the target itself, immediately before or during the treatment. The combination of tightly conforming dose to the target and verification of the target position during the treatment spares a significant portion of the normal tissue from high-dose radiotherapy. **Table 1** gives a brief summary of differences between SBRT and conventional radiotherapy. Stereotactic body radiotherapy is not limited to any particular machine. The ability to deliver high doses accurately and safely is crucial. There are several technologies available for delivery of SBRT to the target volume.

Stereotactic body radiotherapy is now an increasingly prevalent ablative treatment strategy in radiation oncology clinics both at academic and community centers. Treatments generally include delivery of more than 8 Gy per fraction in 1 to 5 fractions, over a period of 1 to 2 weeks. In contrast, conventionally fractionated standard radiotherapy typically uses 1.8 to 2.0 Gy per fraction delivered over a period of 5 to 6 weeks. The main advantage of high dose per fraction radiotherapy is a higher biological potency that results in better local control and tumor response rate. The main disadvantage relates to more pronounced injury to any normal tissues receiving the same potent dose.

Today, SBRT is increasingly being used to treat inoperable early stage primary non–small-cell lung cancer as well as metastatic disease in the lungs and liver from other primary malignancies with a local control at 2 years of over 90% for lung and liver metastases, respectively.[10,11] Patients who have a limited number of metastatic deposits within their body, so-called oligometastases, may be potentially cured if their oligometastases are completely eradicated.[14] While surgical metastatectomy still remains the standard of care in operable patients, SBRT, as a non-invasive approach, is increasingly being used. Stereotactic body radiotherapy can be delivered on an outpatient basis in a short time frame, which allows patients a quick recovery, and return to daily activities.

Renal cell carcinoma has been considered radioresistant. This belief prevails despite the impressive clinical effectiveness of stereotactic radiosurgery used for years in the management of brain metastases from RCC with local control ≥90%.[15-20] Perhaps a similar clinical paradigm exists in extracranial sites. This article provides a critical literature review of SBRT in the management of primary and metastatic RCC. An attempt was made to collect evidence to answer the following questions: Is a high SF_{2Gy}, implying radioresistance, predictive of radioresistance at higher dose per fraction radiotherapy achievable by SBRT? Can cells deemed to be radioresistant at 2 Gy be simultaneously radiosensitive at higher dose?

Materials and Methods

PubMed was searched for English-language publications up to December 2010 on SBRT for primary and metastatic RCC outside the brain. The search was performed using the following key words: renal cell carcinoma, kidney cancer, radiosurgery, stereaotactic radiosurgery, stereotactic body radiation therapy, extracranial stereotactic body radiotherapy, metastatic renal cell carcinoma, and spinal metastases. Ten reports of SBRT for primary and metastatic RCC were identified, and full articles were obtained. Treatment experiences were divided into spinal metastases versus nonspinal metastases (including primary RCC).

Table 1. Differences Between Stereotactic Body Radiotherapy and Conventional Radiotherapy

	Stereotactic body radiotherapy	Conventional radiotherapy
Potency	Very potent, ablative	Typically nonablative, and used in the adjuvant setting to address microscopic disease; it can be ablative if high dose is delivered for a definitive treatment
Dose per fraction	High dose per fraction (≥ 8 Gy)	Low dose per fraction (1.8-2.0 Gy)
Overall treatment time	1-5 treatment fractions over 1-2 weeks	5-9 weeks, for instance, definitive radio therapy for prostate cancer in 44 fractions (each fraction 1.8 Gy) over 9 weeks
Treatment volume definition	Minimal amount of normal tissue may be included in the treatment volume to account for set-up error and tumor motion; there is very limited normal tissue DNA damage repair due to ablative dose	Minimal amount of normal tissue should be included to minimize treatment toxicity; however, low dose per fraction allows normal tissue DNA damage repair
Application	Early stage medically inoperable non–small-cell lung cancer*, lung, and liver metastases from different primary malignancies including kidney cancer, primary small medically inoperable kidney cancer, prostate cancer†	The majority of disease sites in radiation oncology

*SBRT is now the standard of care for early stage medically inoperable non-small cell lung cancer.
†For definitive therapy of prostate cancer, the standard of care in radiation oncology is still conventional radiotherapy, while SBRT is currently used in the setting of a clinical trial only.

Results

SBRT for primary and metastatic RCC (excluding spinal metastases)

Table 2 presents a summary of published SBRT data for primary and metastatic renal cell carcinoma. In 2005, Wersall and colleagues[21] at Karolinska University Hospital reported a retrospective experience in 58 patients with primary and metastatic RCC. The majority of patients underwent nephrectomy, subsequently presented with lung metastases, and received no prior systemic therapy. Primary biopsy-proven RCC was treated in 8 patients. Follow-up strategy included CT every 3 months for 2 years, and then every 6 months. With a median follow-up of 37 months, local tumor control was 90%. The treatment was well tolerated with grade I-II toxicities, such as cough, nausea, and pain; 5 out of 58 patients developed radiation pneumonitis, and only 1 out of 58 patients had grade V toxicity (gastric hemorrhage).

In 2006, the Karolinska University group reported a phase 2 trial of SBRT in patients with primary and metastatic RCC.[22] The primary goal of this study was to evaluate the safety and efficacy of SBRT. The study included 30 patients with a mean age of 64 years. Lung and mediastinal metastases were the most commonly treated tumors. The majority of patients received no prior systemic therapy. Primary RCC was treated in 10 patients. The same follow-up strategy was used as previously reported by Wersall and colleagues.[21] With a median follow-up of 52 months, local tumor control was 79%, and median overall survival was 32 months. Adverse effects were mild, mostly limited to grade I-II toxicities, such as cough, fatigue, and skin rash with local pain.

The Karolinska University group subsequently reported on 2 additional small studies. One study included patients who demonstrated an immunomodulatory effect (also known as abscopal effect) of SBRT in non-irradiated metastases.[23] This effect, characterized by a regression of non-irradiated metastases was seen in 4 out of 28 (14%) patients following SBRT. The authors speculated that radiation therapy might be able to cause a release of tumor antigens, which are recognized by the dendritic cells. These cells, as antigen presenting cells, migrate to the draining lymph nodes and present antigens to T cells with a subsequent immune response. The other study included 7 patients with primary or metastatic RCC with only 1 functioning kidney.[24] In this study, 3 out of 7 patients were alive with a median follow-up of 49 months, and none of the patients developed hypertension or kidney failure that required dialysis.

In the United States, 2 studies in patients with primary and metastatic RCC have been reported. Qian and colleagues[25] reported their experience with 74 patients with the majority of patients treated for metastatic disease. With a median follow-up of 10 months, local tumor control was 92% for patients with metastases, and 93% for patients with primary RCC. Beitler and colleagues[26] published their experience with 9 patients with primary biopsy-proven RCC treated with SBRT. During the median follow-up of 26 months 4 out of 9 patients were alive. Stereotactic body radiotherapy was well tolerated: 2 out of 9 patients experienced nausea and vomiting and 1 out of 9 patients experienced weight loss following SBRT.

Table 2. SBRT for Primary and Metastatic Renal Cell Carcinoma

Study	No. patients	No. treated tumors	Dose regimen	Median follow-up (months)	Local control (%)	Overall survival (months)
Wersall et al[21]	58	162	10 Gy x 3-4 15 Gy x 2-3	37	90	NR
Svedman et al[22]	30	82	10 Gy x 3-4 15 Gy x 2-3	52	79	32
Wersall et al[23]	4	4	8 Gy x 4 15 Gy x 2	NR*	NR	59
Svedman et al[24]	7	7	10 Gy x 3-4	49	NR	3/7 alive
Qian et al[25]	74	141	8 Gy x 5	10-12 (mean)	92	NR
Beitler et al[26]	9	10	8 Gy x 5	27	NR	4/9 alive

SBRT, stereotactic body radiotherapy; NR, not reported.

Table 3. SBRT for Renal Cell Carcinoma Spinal Metastases

Study	No. treated tumors	Dose	Median follow-up (months)	Local control (%)	Pain control (%)
Gerszten et al[27]	60	20 Gy x 1	37	NR	89
Gerszten et al[28]	93	20 Gy x 1	21*	94	87
Yamada et al[29]	21	24 Gy x 1	15*	90	NR
Nguyen et al[30]	55	Mostly 9 Gy x 3	13	82	52

SBRT, stereotactic body radiation; NR, not reported.

*Study was not limited to patients with RCC; reported median follow-up, local control, and pain control are for all patients.

SBRT for spinal metastases from RCC

Table 3 summarizes published data on SBRT for RCC spinal metastases. Several retrospective studies in the United States reported on SBRT outcomes in patients with spinal metastases secondary to RCC. Gerszten and colleagues,[27] at the University of Pittsburgh, reported their experience with 48 patients and 60 treated spinal metastases with 20 Gy in a single fraction. With a median follow-up of 37 months, pain control was 89%.

In a larger study that included spinal metastases from different primary tumors, the same group treated 393 patients with 500 spinal metastatic lesions out of which 93 spinal metastases were in patients with RCC histology.[28] During the median follow-up of 21 months, utilizing 20 Gy in a single fraction, local spinal tumor control was 94% and pain relief was 87%.

Yamada and colleagues,[29] at Memorial Sloan-Kettering Cancer Center, reported their experience with 24 Gy in a single fraction. A total of 93 patients with 103 spinal metastases were treated; 21 out of 103 patients had spinal me-tastases secondary to RCC. With a median follow-up of 15 months, local spinal tumor control and pain relief were 90%. Recently, Nguyen and colleagues[30] at the MD Anderson Cancer Center published their experience with SBRT in patients with spinal metastases secondary to RCC only. Most of the spinal metastases were treated with 21 Gy in 3 fractions. In 48 patients with 55 spinal metastases secondary to RCC during the median follow-up of 13 months, local spinal tumor control was 82% and pain relief 52%.

Discussion

Renal cell carcinoma is considered radioresistant, and this belief prevails despite our experience with stereotactic radiosurgery in patients with brain metastases from primary RCC. While perhaps RCC is radioresistant to 2 Gy fractions, several clinical studies from the United States and Europe reported excellent local control of brain metastases in patients with RCC treated with >10 Gy fractions delivered with stereotactic radiosurgery.[15-20] Reported local control is ≥90% and the majority of patients die of extracranial disease progression. Sheehan and colleagues[20] at the University of Pittsburgh have published one of the largest studies. They reported 96% local brain tumor control in 69 patients who received Gamma Knife radiosurgery with a median tumor dose of 16 Gy in a single fraction.[20] The majority of patients (83 %) died of extracranial disease progression.

Laboratory evidence also challenges the labeling of radioresistance. Efficacy of high-dose-per-fraction radiotherapy for implanted human RCC in a mouse model was shown in a study at the University of Texas Southwestern Medical Center.[31] Nude mice were injected subcutaneously with A498 human RCC cells and the animals were subsequently irradiated with 48 Gy in 3 fractions while untreated animals served as controls. Treatment with high-dose-per-fraction radiotherapy resulted in a sustained decrease in tumor volume, and marked cytological changes with extensive tumor necrosis.

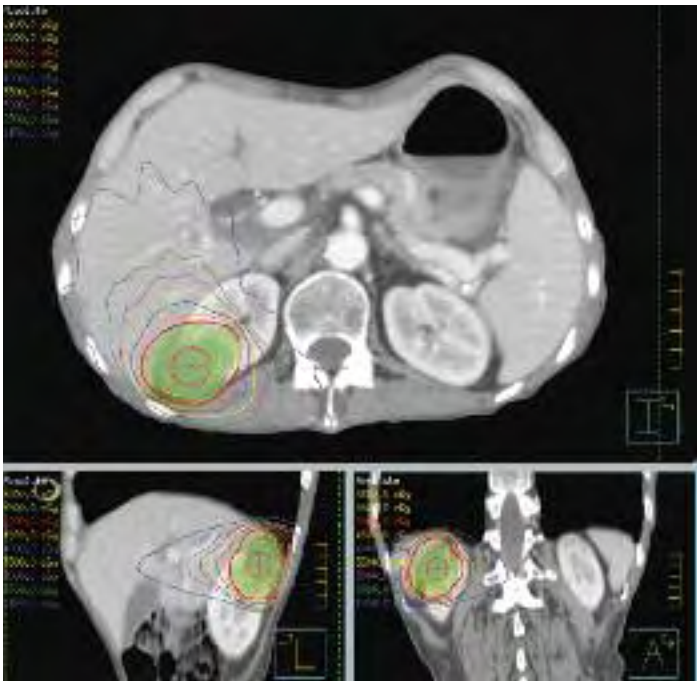

Figure 2. Stereotactic body radiotherapy (SBRT) treatment plan of a 47-year-old man with T1a biopsy-proven renal cell carcinoma (RCC) of the right kidney. The patient was considered medically inoperable because of multiple comorbidites and was not a good candidate for thermal ablation because of the tumor's proximity to the diaphragm. Utilizing SBRT, 50 Gy in 5 fractions was successfully delivered to the planning target volume (primary RCC with 0.5 cm margin). A cross inside a circle represents the treatment isocenter, while thin lines around the circle represent the isodose distribution.

The question remains whether all medically inoperable patients with a small RCC need therapy. Some patients may have an indolent form of RCC, and may not need any treatment. Volpe and colleagues[32] at Princess Margaret Hospital studied the natural history of incidentally detected small renal masses. During the median follow-up of 28 months only 34% of the renal masses grew, which suggests that observation alone may be appropriate for some patients. The elderly patients who are poor surgical candidates with small (< 3 cm), solid, enhancing, homogeneous renal lesions, can be managed with observation and serial renal imaging.[33]

Nephron sparing surgery, thermal ablation therapy, or SBRT can be considered if imaging shows disease progression. **Figure 2** shows an SBRT treatment plan of a medically inoperable patient with T1a biopsy-proven RCC of the right kidney. Serial imaging with MRI demonstrated interval tumor progression before local therapy with SBRT was considered.

Targeted therapy with sorafenib and sunitinib in patients with metastatic RCC has been shown to improve progression-free survival.[34,35] It is unknown whether the addition of these agents following SBRT in patients with oligometastases from RCC can improve in-field local control, out-of-field disease progression, and overall survival in patients with metastatic RCC. Regression of non-irradiated metastases following SBRT indicates a possible immunomodulatory effect (also known as abscopal effect) of SBRT in non-irradiated metastatic deposits.[23] Further studies are necessary to elucidate this clinical phenomenon.

The available phase 2 and retrospective data for primary and metastatic RCC that showed that SBRT yields high local control have been presented. Stereotactic body radiotherapy as a treatment modality should be considered in patients with medically inoperable early stage primary RCC and patients with oligometastases from this malignancy. Patients with local recurrence after other therapies may also be candidates for SBRT. Further prospective clinical trials and dose escalation studies are necessary to clearly establish the role of SBRT in patients with primary RCC.

Conclusions

Available data indicate that RCC, which is considered radioresistant to conventionally fractionated radiation therapy, shows response to SBRT and local control no worse than other histologies. Radioresistance to conventionally fractionated RT, does not necessarily imply radioresistance to high dose fractions. Stereotactic body radiotherapy is a reasonably safe and effective treatment for controlling gross disease from RCC.

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(continued from page 8)

remained after researchers adjusted for factors such as age, sex, and race.

"These results add to growing literature that shows that the hepatitis C virus causes disease that extends beyond the liver," said lead author Stuart C. Gordon, MD, Director of Hepatology at Henry Ford Hospital. Gordon said it is too early to determine whether more kidney cancer screening of people with hepatitis C is needed. "However, a heightened awareness of an increased kidney cancer risk should dictate more careful follow-up of incidental renal [kidney] defects when detected on imaging procedures in patients with chronic hepatitis C," Dr Gordon stated. The study appeared in the journal *Cancer Epidemiology, Biomarkers & Prevention*.

Newly discovered mutations may help drive common kidney cancer

HINXTON, UK—Researchers have discovered mutations in the gene *PBRM1* in more than one-third of clear cell renal cell carcinomas (ccRCC), the most common kidney cancer. In a series of experiments led by Dr Ignacio Varela of the Wellcome Trust Sanger Institute, an international team of researchers identified *PBRM1* as a potential tumor suppressor gene and showed that the loss of the gene's function may contribute to kidney cells developing the properties of cancer cells, such as uncontrolled cell growth. The findings appeared online in *Nature*.

The scientists first sequenced portions of the genome known to produce proteins (the exome) in 7 ccRCC tumor samples and normal tissue from the same patients. They identified 156 mutations in the 7 samples, but only mutations in the *PBRM1* gene were found in more than 1 sample. They next sequenced the *PBRM1* gene in an additional 257 RCC samples (including 36 non-ccRCC cases) and found mutations in 88 samples (all ccRCC), a frequency that the authors described as "remarkable." The researchers also found *PBRM1* gene mutations in breast, lung, kidney, gallbladder, and pancreatic cancer cell lines. Analysis of genetic data from a mouse model of pancreatic cancer indicate that inactivation of the *PBRM1* gene may help drive pancreatic tumor development in this model.

Using small interfering RNAs to block *PBRM1* gene activity in ccRCC cells, the researchers were able to increase cell proliferation cell-colony formation (the ability to grow and divide without physical support), and cell movement. Similar to that required for metastasis, *PBRM1* codes for a protein that is involved in chromatin remodeling, a process that allows transcription factors to gain access to DNA that is otherwise tightly packaged with proteins. According to the researchers, analysis of the cell-signaling pathways regulated by *PBRM1* suggests that, "*PBRM1*activity regulates pathways associated with chromosomal instability and cellular proliferation." They also noted that several other genes that have been implicated in ccRCC are involved in chromatin remodeling. "This is very promising, very exciting work," commented Marston Linehan, MD, Chief of the Urologic Oncology Branch in NCI's Center for Cancer Research. Dr Linehan was part of the scientific team that identified the tumor suppressor gene *VHL*, which is the only other gene known to play a role in a large number of ccRCC cases. He concluded that "This finding leads us potentially into a whole new direction in thinking about the basic aspects of kidney cancer and potential approaches to therapy. It's possible that mutations in *PBRM1* are a critical part of clear-cell kidney cancer and that you need both *VHL* and *PBRM1* to be altered to develop a clear-cell kidney cancer." KCJ

(continued from page 9)

prospective analysis. Thyroid function was assessed in each patient every 4 weeks during the first 2 months of treatment and every 2 to 4 months thereafter. Assessment included serum levels of thyroid-stimulating hormone (TSH), tri-iodthyronine (T3), and thyroxine (T4). Subclinical hypothyroidism was defined as an increase in TSH above the upper limit of normal (>3.77 M/mL) with normal T3 and T4 levels. Subclinical hypothyroidism was evident in 5 patients at baseline and occurred in 30 patients (36.1%) within the first 2 months after treatment initiation. There was a statistically significant correlation between the occurrence of subclinical hypothyroidism during treatment and the rate of objective remission (hypothyroid patients vs euthyroid patients: 28.3% vs 3.3%, respectively; $P < .001$) and the median duration of survival (not reached vs 13.9 months, respectively; hazard ratio, 0.35; 95% confidence interval, 0.14-0.85; $P = .016$). In multivariate analysis, the development of subclinical hypothyroidism was identified as an independent predictor of survival (hazard ratio, 0.31; $P = .014$).
Conclusion: Hypothyroidism may serve as a predictive marker of treatment outcome in patients with mRCC. Thus, the interpretation of hypothyroidism during treatment with sunitinib and sorafenib as an unwanted side effect should be reconsidered.

Metastasectomy after targeted therapy in patients with advanced renal cell carcinoma.

Karam JA, Rini BI, Varella L, et al. ***Journal of Urology*****. 2011;185:439-44.**
Summary: This study retrospectively evaluated the records of patients who underwent consolidative metastasectomy after targeted therapy at 3 institutions from 2004 to 2009. All patients received at least 1 cycle of targeted therapy before surgical resection of all visible disease. The authors identified 22 patients. Metastasectomy sites included the retroperitoneum in 12 patients, lung in 6, adrenal gland in 2, bowel in 2, and mediastinum, bone, brain and inferior venal caval thrombus in 1 each. A total of 6 postoperative complications were observed in 4 patients within 12 weeks after surgery, which resolved with appropriate management. Postoperatively 9 patients received at least 1 targeted therapy. In 11 patients recurrence developed a median of 42 weeks after metastasectomy and another 11 experienced no recurrence at a median of 43 weeks. At a median followup of 109 weeks 21 patients were alive and 1 died of renal cell carcinoma 105 weeks after metastasectomy.
Conclusion: In a cohort of select patients with a limited tumor burden after treatment with targeted agents consolidative metastasectomy is feasible with acceptable morbidity. Significant time off targeted therapy and long-term tumor-free status are possible with this approach.

The impact of cytoreductive nephrectomy on survival of patients with metastatic renal cell carcinoma receiving vascular endothelial growth factor targeted therapy.

Choueiri TK, Xie W, Kollmannsberger C, et al. ***Journal of Urology*****. 2011;185:60-6.**
Summary: The role of cytoreductive nephrectomy in the era of novel agents remains poorly defined. This study retrospectively reviewed baseline characteristics and outcomes of 314 patients with anti-vascular endothelial growth factor therapy naive, metastatic renal cell carcinoma from United States and Canadian cancer centers to study the impact of cytoreductive nephrectomy on overall survival. Patients who underwent cytoreductive nephrectomy (201) were younger ($P < 0.01$), and more likely to have a better Karnofsky performance status ($P < 0.01$), more than 1 site of metastasis ($p = 0.04$) and lower corrected calcium levels ($P < 0.01$) compared to those who did not undergo cytoreductive nephrectomy (113). On univariable analysis cytoreductive nephrectomy was associated with a median overall survival of 19.8 months compared to 9.4 months for patients who did not undergo cytoreductive nephrectomy (HR 0.44; 95% CI 0.32, 0.59; $P < 0.01$). On multivariable analysis and adjusting for established prognostic risk factors the overall survival difference persisted (adjusted HR 0.68; 95% CI 0.46, 0.99; $P = 0.04$) in favor of the cytoreductive nephrectomy group. In subgroup analyses stratified for favorable/intermediate/poor risk criteria, patients in the poor risk group had a marginal benefit ($P = 0.06$). Similarly patients with Karnofsky performance status less than 80% also had a marginal survival benefit ($P = 0.08$).
Conclusion: In this retrospective study cytoreductive nephrectomy was independently associated with a prolonged overall survival of patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor targeted agents, although the benefit is marginal in those patients with poor risk features. KCJ

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are likely to see treatment options tailored according to the specific needs of the individual patient. a shift in the treatment paradigm for RCC . Among the key questions to be addressed by future trials will be identification and inhibition of additional pathways important for RCC pathogenesis and resistance, and how best to inhibit these. This may be investigated by combinations of selective agents (ex. tivozanib) with other agents or one agent by multi-targeted approach (ex. Dovitinib). the role of these agents beyond monotherapy because resistance to VEGF inhibition remains a problem with any of the anti-VEGF compounds so far introduced. New trials will need to further explore the role of new targeted therapies in combination with existing treatments or determine the optimal sequencing of these drugs in RCC refractory to standard regimens. Strategies evaluating complete VEGF blockade are needed to test whether we can achieve durable, complete responses in patients with RCC with VEGF-targeted therapies.

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