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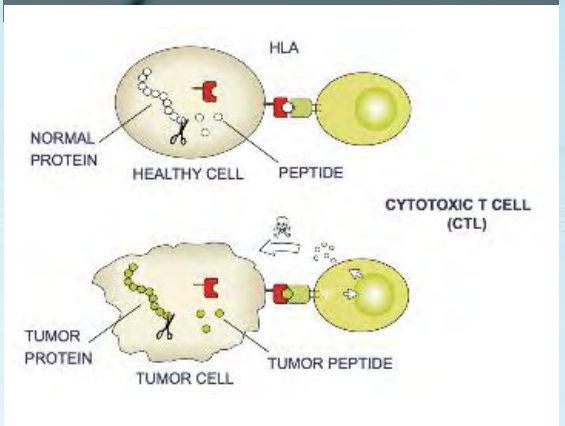
A New Day in Treatment: Here Come the Vaccines



Also in this Issue:

Antiangiogenic Therapies in Elderly RCC Patients

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

SUTENT® (sunitinib malate) 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 A NEARLY 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 mRCC.

mRCC=metastatic renal cell carcinoma; 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 pages.

Important Safety Information

Hepatotoxicity has been observed in clinical trials and post-marketing experience. This hepatotoxicity may be severe, and deaths have been reported. Monitor liver function tests before initiation of treatment, during each cycle of treatment, and as clinically indicated. SUTENT should be interrupted for Grade 3 or 4 drug-related hepatic adverse events and discontinued if there is no resolution. Do not restart SUTENT if patients subsequently experience severe changes in liver function tests or have other signs and symptoms of liver failure.

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

Cardiovascular events, including heart failure, myocardial disorders, and cardiomyopathy, some of which were fatal, have been reported through post-marketing experience. Monitor patients for signs and symptoms of congestive heart failure (CHF) and, in the presence of clinical manifestations, discontinuation is recommended. Patients who presented with cardiac events, pulmonary embolism, or cerebrovascular events within the previous 12 months were excluded from clinical studies.

SUTENT has been shown to prolong QT interval in a dose-dependent manner, which may lead to an increased risk for ventricular arrhythmias including torsades de pointes, which has been seen in <0.1% of patients. Monitoring with on-treatment electrocardiograms and electrolytes should be considered.

Hypertension may occur. Monitor blood pressure and treat as needed with standard antihypertensive therapy. In cases of severe hypertension, temporary suspension of SUTENT is recommended until hypertension is controlled.

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.

Cases of impaired wound healing have been reported during SUTENT therapy. Temporary interruption of therapy with SUTENT is recommended in patients undergoing major surgical procedures.

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

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

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

The most common grade 3/4 ARs (occurring in ≥5% of patients with RCC receiving SUTENT vs IFNα) 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 with RCC 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]*

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

DOSAGE AND ADMINISTRATION

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

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

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS

Hepatotoxicity. SUTENT has been associated with hepatotoxicity, which may result in liver failure or death. Liver failure has been observed in clinical trials (7/2281 [0.3%]) and post-marketing experience. Liver failure signs include jaundice, elevated transaminases and/or hyperbilirubinemia in conjunction with encephalopathy, coagulopathy, and/or renal failure. Monitor liver function tests (ALT, AST, bilirubin) before initiation of treatment, during each cycle of treatment, and as clinically indicated. SUTENT should be interrupted for Grade 3 or 4 drug-related hepatic adverse events and discontinued if there is no resolution. Do not restart SUTENT if patients subsequently experience severe changes in liver function tests or have other signs and symptoms of liver failure.
Safety in patients with ALT or AST >2.5 x ULN or, if due to liver metastases, >5.0 x ULN has not been established.

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

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 interferon-α (IFN-α). In the treatment-naïve RCC study, 103/375 (27%) and 54/360 (15%) patients on SUTENT and IFN-α, respectively, had an LVEF value below the LLN. Twenty-six patients on SUTENT (7%) and seven on IFN-α (2%) experienced declines in LVEF to >20% below baseline and to below 50%. Left ventricular dysfunction was reported in four patients (1%) and CHF in two patients (<1%) who received SUTENT.
Patients who presented with cardiac events within 12 months prior to SUTENT administration, such as myocardial infarction (including severe/unstable angina), coronary/peripheral artery bypass graft, symptomatic CHF, cerebrovascular accident or transient ischemic attack, or pulmonary embolism were excluded from SUTENT clinical studies. It is unknown whether patients with these concomitant conditions may be at a higher risk of developing drug-related left ventricular dysfunction. Physicians are advised to weigh this risk against the potential benefits of the drug. **These patients should be carefully monitored for clinical signs and symptoms of CHF while receiving SUTENT. Baseline and periodic evaluations of LVEF should also be considered while these patients are receiving SUTENT. In patients without cardiac risk factors, a baseline evaluation of ejection fraction should be considered.**

QT Interval Prolongation and Torsade de Pointes. SUTENT has been shown to prolong the QT interval in a dose dependent manner, which may lead to an increased risk for ventricular arrhythmias including Torsade de Pointes. Torsade de Pointes has been observed in <0.1% of SUTENT-exposed patients.
SUTENT should be used with caution in patients with a history of QT interval prolongation, patients who are taking antiarrhythmics, or patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances. When using SUTENT, periodic monitoring with on-treatment electrocardiograms and electrolytes (magnesium, potassium) should be considered. Concomitant treatment with strong CYP3A4 inhibitors, which may increase sunitinib plasma concentrations, should be used with caution and dose reduction of SUTENT should be considered *[see Dosage and Administration]*.

Hypertension. Patients should be monitored for hypertension and treated as needed with standard anti-hypertensive therapy. In cases of severe hypertension, temporary suspension of SUTENT is recommended until hypertension is controlled.
Of patients receiving SUTENT for treatment-naïve RCC, 127/375 patients (34%) receiving SUTENT compared with 13/360 patients (4%) on IFN-α experienced hypertension. Grade 3 hypertension was observed in 50/375 treatment-naïve RCC patients (13%) on SUTENT compared to 1/360 patients (<1%) on IFN-α. No Grade 4 hypertension was reported. SUTENT dosing was reduced or temporarily delayed for hypertension in 21/375 patients (6%) on the treatment-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 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.

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

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

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

ADVERSE REACTIONS

The data described below reflect exposure to SUTENT in 660 patients who participated in the double-blind treatment phase of a placebo-controlled trial (n=202) for the treatment of gastrointestinal stromal tumor (GIST), an active-controlled trial (n=375) for the treatment of RCC or a placebo-controlled trial (n=83) for the treatment of pancreatic neuroendocrine tumors (pNET). The RCC patients received a starting oral dose of 50 mg daily on Schedule 4/2 in repeated cycles.
The most common adverse reactions (≥20%) in patients with GIST, RCC or pNET are fatigue, asthenia, fever, diarrhea, nausea, mucositis/stomatitis, vomiting, dyspepsia, abdominal pain, constipation, hypertension, peripheral edema, rash, hand-foot syndrome, skin discoloration, dry skin, hair color changes, altered taste, headache, back pain, arthralgia, extremity pain, cough, dyspnea, anorexia, and bleeding. The potentially serious adverse reactions of hepatotoxicity, left ventricular dysfunction, QT interval prolongation, hemorrhage, hypertension, thyroid dysfunction, and adrenal function are discussed in *Warnings and Precautions*. Other adverse reactions occurring in RCC studies are described below.
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse Reactions in the Treatment-Naïve RCC Study. The as-treated patient population for the treatment-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. Cases of arterial thromboembolic events, sometimes fatal, have been reported in patients treated with SUTENT. The most frequent events included cerebrovascular accident, transient ischemic attack and cerebral infarction.

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

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

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

USE IN SPECIFIC POPULATIONS

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

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

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

Nursing Mothers. Sunitinib and its metabolites are excreted in rat milk. In lactating female rats administered 15 mg/kg, sunitinib and its metabolites were extensively excreted in milk at concentrations up to 12-fold higher than in plasma. It is not known whether this drug or its primary active metabolite are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from SUTENT, a decision should be made whether to discontinue nursing or to discontinue the drug taking into account the importance of the drug to the mother.

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

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

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

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

OVERDOSAGE

Treatment of overdose with SUTENT should consist of general supportive measures. There is no specific antidote for overdosage with SUTENT. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage. 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. The carcinogenic potential of sunitinib has been evaluated in rasH2 transgenic mice. Gastroduodenal carcinomas and/or gastric mucosal hyperplasia, as well as an increased incidence of background hemangiosarcomas have been observed at doses of ≥25 mg/kg/day (approximately 7 times the AUC in patients administered the RDD of 50 mg/day) following daily dose administration of 1- or 6-months duration. No proliferative changes were observed in rasH2 transgenic mice at 8 mg/kg/day. Sunitinib did not cause genetic damage when tested in *in vitro* assays (bacterial mutation [AMES Assay], human lymphocyte chromosome aberration) and an *in vivo* rat bone marrow micronucleus test.

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

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

PATIENT COUNSELING INFORMATION

Gastrointestinal Disorders. Gastrointestinal disorders such as diarrhea, nausea, stomatitis, dyspepsia, and vomiting were the most commonly reported gastrointestinal events occurring 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

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Kidney Cancer Journal Author Guidelines

Scope of Manuscripts

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

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

Manuscript Submission

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

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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.

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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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About the Cover
Phase 3 trials are evaluating the use of multipeptide vaccines in renal cell carcinoma, ushering in what could be a new era in treatment that combines vaccine with a tyrosine kinase inhibitor. Cellular interactions are depicted in this conceptual illustration and are further elucidated in the article on vaccine therapy, page 106. (Copyright 2012, Photo Researchers)

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KCJ EDITOR'S MEMO

Will a Renaissance in Immunotherapy Become Part of the Paradigm of Cancer Care?

Robert A. Figlin, MD

Inundated with all the predictions of what cancer care will look like in the future, it would be easy for us to speculate on what may transpire and how we will get there. It remains to be seen how soon some of the futuristic visions may become reality. For example, in one such scenario, involving a newly diagnosed kidney cancer, a patient is studied in a trial involving two new drugs attached to a microscopic "nanoparticle shuttle" that will deliver them directly to individual cancer cells, sparing healthy cells and minimizing side effects.

This is not from a Star Wars-like vision of future care, it's actually contained in a recently issued report, *ASCO's Blueprint for Transforming Clinical and Translational Cancer Research,* issued late last year.[1] If you want to see where cancer care is headed, please read the report available on the ASCO website. The Blueprint presents a vision for the next decade, in which cancer research and patient care become significantly more targeted, more efficient and more effective. It urges that we:

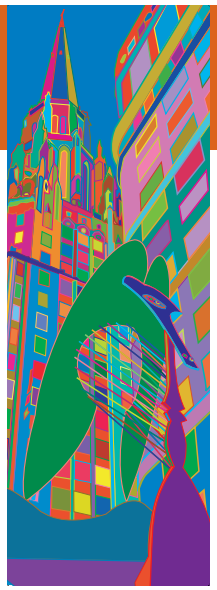
Establish a new approach to therapeutic development, driven by our more thorough understanding of cancer biology and the advent of new technologies.
- Identify and prioritize the molecular targets that have the greatest promise to improve survival
- Incentivize collaboration to encourage industry and researchers to pursue high-priority targeted therapies and diagnostics in combination
- Ensure more aggressive and timely development of biomarkers and diagnostic tests to guide treatment decisions and speed research

2. Design smarter, faster clinical trials to provide evidence for effective treatments targeted to patients most likely to benefit, sooner:
- Prioritize trials with the greatest potential benefits for patients, or that address clear unmet needs; shift away from trials that promise only marginal improvements in care
- Develop shared standards for flexible trial designs that allow researchers to demonstrate results with smaller populations defined by specific molecular characteristics
- Select trial participants primarily based on molecular characteristics, to ensure that only those who are most likely to benefit are included, and that patients aren't excluded from trials because of health conditions that aren't relevant

Edward Jenner

Considered the Father of Immunology

This is one way of looking at the future. Another way to grasp where cancer care is headed is to read the content on active immunotherapy in this issue of the Kidney Cancer Journal How timely is it? One of the topics at this year's ASCO GU Symposium is the *Renaissance in Immunotherapy*, suggesting how the use of high-dose interleukin-2 has become more sophisticated in the appropriate selection of patients. *(continued on page 126)*



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

Argos Therapeutics to Initiate Late-Stage Trial for AGS-003 in Combination With Sunitinib in Metastatic RCC

DURHAM, NC—Argos Therapeutics, Inc., is planning to initiate a phase 3 clinical trial, referred to as the ADAPT study, to evaluate the combination of AGS-003 with sunitinib in patients with newly diagnosed, previously untreated, metastatic RCC (mRCC).

AGS-003 is a personalized immunotherapy comprised of tumor RNA loaded dendritic cells (DCs), which are designed to stimulate the proliferation of memory T cells targeted to each patient's tumor. AGS-003 is produced for each patient by obtaining a small tumor sample, to isolate and amplify mRNA, along with monocytes derived from a single leukapheresis. Once the monocytes have been differentiated into DCs, they are co-electroporated with RCC and CD40L RNA, vialed and then frozen for future administration. With these starting materials and proprietary manufacturing processes, up to five years of personalized treatment can be generated for each patient.

Argos recently reported results from an open label phase 2 study, which evaluated AGS-003 in combination with sunitinib in 21 patients with newly diagnosed, unfavorable risk mRCC. Updated results from this study were presented in an oral session by Robert Figlin, MD, during the 2012 ASCO Genitourinary Cancers Symposium. In addition to encouraging clinical and immunologic responses, as well as a median progression free survival (PFS) of 11.2 months in this group of intermediate and poor risk mRCC patients, the Kaplan-Meier estimated median overall survival (OS) was 29.3 months, as of January 2012. This prolonged survival was encouraging, since it is longer than has been reported with sunitinib alone in similar risk patients. Furthermore, AGS-003 appears to be readily combinable with sunitinib, as there were no immunotherapy related serious adverse events reported in this study.

The phase 3 ADAPT study is designed to enroll approximately 450 patients with newly diagnosed, unfavorable risk, clear cell mRCC. Patients will be randomized in a 2:1 fashion to the combination of AGS-003 plus standard therapy versus standard therapy alone. Standard therapy will initiate with sunitinib for all patients, however other agents will be permitted on study for those who experience early progression or intolerance to sunitinib. The primary endpoint will be OS, while clinical and immune response rates, safety and PFS will represent key secondary endpoints.

The study will be led by Dr Figlin, MD (Cedars-Sinai Samuel Oschin Comprehensive Cancer Institute, Los Angeles, CA) and Christopher Wood, MD (MD Anderson Cancer Center, Houston, TX). For further information about ADAPT, please contact the company directly via email at contact@adapt-study.com or visit the company website at www.argostherapeutics.com.

Tivozanib demonstrates superiority over sorafenib in patients with advanced renal cell cancer in Phase 3 TIVO-1 trial

CAMBRIDGE, MA —AVEO Pharmaceuticals, Inc. and Astellas Pharma Inc. announced that tivozanib demonstrated superiority over sorafenib in the primary endpoint of progression-free survival (PFS) in TIVO-1, a global, randomized Phase 3 clinical trial evaluating the efficacy and safety of investigational drug tivozanib compared to sorafenib in 517 patients with advanced renal cell carcinoma (RCC). TIVO-1 is the first registration study in first-line RCC that is comparing an investigational agent against an approved VEGF therapy.

All patients in TIVO-1 had clear cell RCC, had undergone a prior nephrectomy, and had not previously been treated with either a VEGF or mTOR therapy. Based on the top-line analysis of events in TIVO-1, determined by a blinded, independent review committee, key top-line findings include:

- tivozanib demonstrated a statistically significant improvement in PFS with a median PFS of 11.9 months compared to a median PFS of 9.1 months for sorafenib in the overall study population.
- tivozanib demonstrated a statistically significant improvement in PFS with a median PFS of 12.7 months compared to a median PFS of 9.1 months for sorafenib in the prespecified subpopulation of patients who were treatment naïve (no prior systemic anti-cancer therapy); this subpopulation was approximately 70% of the total study population.
- tivozanib demonstrated a well-tolerated safety profile consistent with the Phase 2 experience; the most commonly reported side effect was hypertension, a well established on-target and manageable effect of VEGFR inhibitors.

Based on these data, AVEO and Astellas currently plan to submit for marketing approval of tivozanib in the United States and Europe in 2012, subject to final collection and analyses of all available data from the trial. The study participants continue to be observed to gather additional data for further analyses. AVEO and Astellas plan to submit

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Essential Peer-Reviewed Reading in Kidney Cancer

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

Analyzing genetic factors and their potential for targeted therapy

Dondeti VR, Wubbenhorst B, Lal P, et al. Integrative Genomic Analyses of Sporadic Clear Cell Renal Cell Carcinoma Define Disease Subtypes and Potential New Therapeutic Targets. *Cancer Res*. 2011;72(1); 112–21.

Summary: Sporadic clear cell renal cell carcinoma (ccRCC), the most common type of adult kidney cancer, is often associated with genomic copy number aberrations on chromosomes 3p and 5q. Aberrations on chromosome 3p are associated with inactivation of the tumor suppressor gene von-Hippel Lindau (*VHL*), which activates the hypoxia-inducible factors HIF1 and HIF2 . In contrast, ccRCC genes on chromosome 5q remain to be defined. In this study, we conducted an integrated analysis of high-density copy number and gene expression data for 54 sporadic ccRCC tumors that identified the secreted glycoprotein *STC2* (stanniocalcin 2) and the proteoglycan *VCAN* (versican) as potential 5q oncogenes in ccRCCs. In functional assays, *STC2* and *VCAN* each promoted tumorigenesis by inhibiting cell death. Using the same approach, we also investigated the two *VHL*-deficient subtypes of ccRCC, which express both HIF1 and HIF2 (H1H2) or only HIF2 (H2). This analysis revealed a distinct pattern of genomic aberrations in each group, with the H1H2 group displaying, on average, a more aberrant genome than the H2 group.

Conclusion: The findings provide a significant advance in understanding ccRCCs by offering a molecular definition of two subtypes with distinct characteristics as well as two potential chromosome 5q oncogenes, the overexpression of which is sufficient to promote tumorigenesis by limiting cell death.

Managing adverse events associated with targeted therapy

Targeted Therapies for Renal Cell Carcinoma: Review of Adverse Event Management Strategies. Eisen T, Sternberg C, Robert C, et al. *J Nat Cancer Inst*. 2012; Jan.10;Epub ahead of print.

Summary: With the advent of targeted agents for the treatment of renal cell carcinoma (RCC), overall survival has improved, and patients are being treated continuously for increasingly long periods of time. This has raised challenges in the management of adverse events (AEs) associated with the six targeted agents approved in RCC—sorafenib, sunitinib, pazopanib, bevacizumab (in combination with interferon alpha), temsirolimus, and everolimus. Suggestions for monitoring and managing AEs have been published, but there are few consensus recommendations. In addition, there is a risk that patients will be subjected to multiple unnecessary investigations. This review aimed to identify the level of supporting evidence for suggested AE management strategies to provide practical guidance on essential monitoring and management that should be undertaken when using targeted agents. Five databases were systematically searched for relevant English language articles (including American Society of Clinical Oncology abstracts) published between January 2007 and March 2011; European Society of Medical Oncology congress abstracts were hand searched. Strategies for AE management were summarized and categorized according to the level of recommendation. A total of 107 articles were identified that describe a large number of different investigations for monitoring AEs and interventions for AE management.

Conclusion: The authors identify and summarize clear recommendations for the management of dermatologic, gastrointestinal, thyroid, cardiovascular, and other AEs, based predominantly on expert opinion. However, because the evidence for the suggested management strategies is largely anecdotal, there is a need for further systematic investigation of management strategies for AEs related to targeted therapies for RCC.

New data assess diabetes as a risk factor for RCC

***Diabetes and Risk of Renal Cell Carcinoma*.**

Habib SL, Prihoda TJ, Luna M, et al. Diabetes and Renal Cell Carcinoma. *J Cancer* 2012; 3: 42-48.

Summary: There is evidence that the incidence of solid tumors is markedly increased in patients with diabetes mellitus. This study investigated the association between diabetes and renal cancer. A single-center retrospective analysis of 473 patients who underwent nephrectomy for renal cell carcinoma (RCC) was performed. Diabetic RCC patients were screened for age, gender, ethnicity, HgA1C, glucose levels and renal function. Of the 473 cases with RCC, we identified 120 patients (25.4%) with a history of diabetes. The incidence of diabetes in RCC patients was higher in female than male subjects and in Hispanic compared to white and other ethnic backgrounds. At diagnosis, the majority of diabetic RCC patients were 50-59 years of age. In diabetic RCC cases, clear cell type histology (92.0%), nuclear grade 2 (56.1%) and tumor size range from 1-5 cm (65.7%) were the most common in each category.

Conclusion: Diabetic RCC patients have a predominance of localized, small clear cell RCC. In addition, females with a history of RCC have a higher frequency of diabetes compared to males. This is the first report of clinical and histopathological features of RCC associated with diabetes.

Encouraging results suggest complete remissions in some cases with TKIs

Complete Remission With Tyrosine Kinase Inhibitors in Renal Cell Carcinoma. Albiges L, Oudard S, Negrier S, et al. *J Clin Oncol*. 2012 Jan 9 [Epub ahead of print]

Summary: Complete remission (CR) is uncommon during treatment for metastatic renal cell carcinoma (mRCC) with tyrosine kinase inhibitors (TKIs), but it may occur in some patients. It remains a matter of debate whether ther-

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Dawn of a New Day in Therapy: Here Come the Vaccines

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Immunotherapeutic approaches implementing tumor-based vaccines are making significant headway and within the foreseeable future could move from the bench to the bedside. The focus of clinical trials is to validate well-defined vaccines targeting the induction of antigen-specific cellular immunity in renal cell carcinoma. This review summarizes efforts to achieve these goals with a vaccine in development and under study in an international trial.

Three potentially distinct targets and related therapeutic approaches are currently available in metastatic renal cell carcinoma (RCC): immunotherapy, vascular endothelial growth factor (VEGF) pathway blockade, and mTOR inhibition. Following the approval of 6 novel targeted agents since December 2005 and limited comparative trials to discern relative efficacy, the treatment of metastatic RCC has become immensely complex. [1]

Historically, immunotherapy was the principal treatment option for patients with metastatic RCC with only a limited subset of patients experiencing a long-term clinical benefit. In recent years, because of an improved understanding of the molecular mechanisms underlying RCC, particularly the unique relationship between RCC and angiogenesis, effective targeted therapies have emerged. Currently, the VEGF tyrosine kinase inhibitors (TKIs) sunitinib, pazopanib, and sorafenib, the anti-VEGF monoclonal antibody bevacizumab, as well as the rapamycin analogues temsirolimus and everolimus, have been approved for use in the United States in the treatment of patients with metastatic RCC.

Ongoing clinical trials are evaluating a broad spectrum of approaches to RCC, including the use of sequential and combination therapies. A new generation of treatments still undergoing Phase 3 evaluation, including TKIs such as axitinib and tivozanib, which are more selective against VEGFR and biochemically more potent, has also raised hopes that the side effect profile of these agents may also improve while prolonging progression free survival. Despite these dramatic advances in therapy—part of what has often been called a "revolution" in treatment—many questions remain regarding their use. One major consideration is the lack of curative targeted therapy and the need for chronic, ongoing treatment. In this light, immunotherapy has been revisited with new approaches.

Keywords: Immunotherapy, vaccination, renal cell carcinoma, immunology, tumor-associated peptides.

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Role of Immunotherapy: Revisiting the Roots of RCC Treatment

The responsiveness of metastatic RCC to immune-stimulating agents has been known for many years. Low rates of objective tumor regression have been reported consistently in clinical trials of cancer vaccines and various cytokines. Of the cytokines, interferon-alpha and interleukin-2 (IL-2) appear to demonstrate the highest response rates, in the range of 5-20%, and therefore have been studied extensively alone and in combination with other agents (4) High dose IL-2 in particular produces durable complete remissions in approximately 5% of patients with mRCC , including patients with large tumor burdens, and thus provides important proof-of-concept for the therapeutic potential of immunotherapy in this disease.[2]

The immunologic mechanisms by which IL-2 produces tumor regression in mRCC are not fully understood. Nevertheless, it seems reasonable to assume that IL-2 and other immune therapies are activating or expanding T-lymphocytes that specifically recognize antigens expressed by renal carcinoma. Further promoting the development, expansion, and effector function of these tumor-specific lymphocytes could lead to even better anti-tumor responses. In line with this hypothesis, several groups have attempted to immunize patients against their tumor. Only a limited number of broadly expressed defined cancer-associated antigens have been identified in renal carcinoma, therefore several cancer vaccines have used allogeneic or autologous tumor cells as the source of antigen, and have relied on advances in immunology (for example, derivation of autologous heat shock protein containing potential peptide antigens, or fusions of dendritic cells with tumor cells) trying to produce more effective T-cell responses to the vaccine antigens. [3,4,5,6]

Until now, so far modest success of cancer vaccines and cytokine therapy is not surprising, when viewed in the context of a more modern understanding of the extensive and complex regulation of immune responses, and the immune inhibitory influences within the tumor

microenvironment. The identification of multiple positive and negative regulators of T-cell activation and function provides new opportunities for effectively modulating anti-tumor immune responses in mRCC. New regulatory immune cell types called regulatory T cells and myeloid-derived suppressor cells have been identified recently. These cells seem to play a vital role in counteracting against tumor control by the immune system. Combination of immunotherapy with novel immunomodulators and agents affecting these regulatory cell types may substantially increase the clinical benefit of cancer vaccines.

Additionally, most molecularly defined immunotherapy approaches have restricted themselves to single (and often invalidated) antigens. Targeting just a single antigen creates an opportunity for the tumor to escape the antigen-specific immune response by downmodulation of the targeted antigen on the tumor surface.[7] Thus, approaches using multiple antigens are expected to be more efficacious than single-antigen approaches.[8]

Active Immunotherapy in RCC: The Rationale

As renal cell carcinoma represents one of the most immune-responsive cancers, immunotherapy exhibits a suitable treatment basis. Beside nonspecific stimulation via cytokines, passive specific and active immunotherapy are also considered appropriate options to recognize and destroy tumor cells.[9] For more than 30 years, research regarding vaccination therapy has been of special interest for the treatment of renal cell carcinoma. However, apart from occasional promising results in Phase I and II trials, vaccination therapy is still considered experimental in this tumor entity, especially owing to missing results from Phase III trials proving clinical efficacy.[9]

The cellular immune response to RCC. The vast majority of antitumor T cells recognize tumor antigens as short protein fragments or peptides presented on the tumor cell surface by major histocompatibility complex (MHC) class I (present 8–12 amino acid long peptides) and class II (present somewhat longer peptides up to approximately 35 amino acids in length) molecules.[10-14] The MHC of humans is called Human Leucocyte Antigen (HLA).

These peptides may derive from virtually any proteins synthesized by the tumor cell (ie, proteins that are found in the nucleus, cytoplasm, lysosome, plasma membrane, or that are secreted) only a small number of which might represent "tumor-associated" or "tumor-specific "sequences. Although still located within intracellular compartments (**Figure 1**), these tumor peptides associate with nascent MHC class I or class II molecules and are subsequently transported to the cell surface where they become accessible to CD8+ and CD4+ T-cell scrutiny, respectively.[15,16]

The ability of a given peptide to bind to, and be presented by, a given MHC allele is determined by structural motifs within the peptide sequence (defining a "peptide binding motif") that allow for sufficient compatibility between peptide amino acid side-chains and micropockets formed within the peptide-binding groove of the MHC molecule.[17-20] This degree of intermolecular compatibility determines the affinity of peptide for an individual MHC molecule, the corresponding half-life of such stable complexes and, to a large degree, the likelihood that the peptide-MHC complex is immunogenic to the existent T-cell repertoire.[21,22,23] Overall, only a limited number (i.e., 1–200) of specific peptide-MHC complexes need to be expressed by a tumor cell target to allow for T-cell effector function to be induced.[24,25]

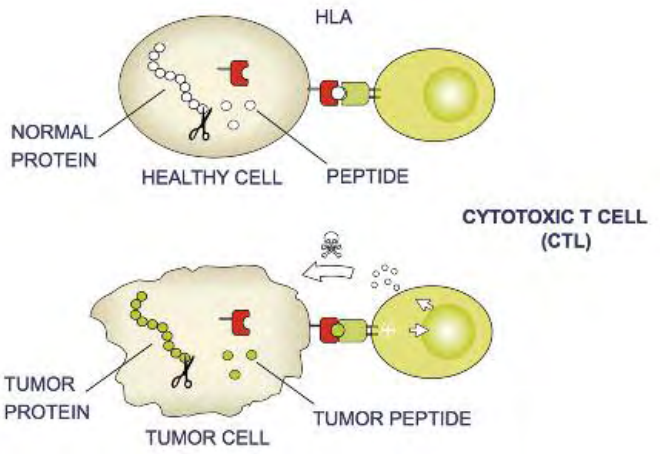

Figure 1.

Role of Tumor-Associated Peptides

Tumor-associated peptides (TUMAPs) are derived from antigens overexpressed on tumor cells. When patients are vaccinated with TUMAPs their T cells become activated to attack and destroy cells specifically expressing these tumor-associated peptides. Although TUMAPs are presented by most tumor cells, T cells are usually in a dormant state in cancer patients because normal tissue- and also tumor cells derived from normal tissue are not inherently capable of stimulating cells of the immune system on its own. At the molecular level, this inability to stimulate T cells is largely due to the absence of certain co-stimulatory surface-standing molecules. The administration or immunization of TUMAPs is aimed at activating or priming T cells in the context of so-called professional antigen-presenting cells (ie, dendritic cells) which harbor the relevant co-stimulatory surface-standing molecules. Those activated T cells will then specifically recognize the corresponding TUMAPs on the surface of tumor cells. Since this immune response is targeting antigens overexposed in the tumor tissue, it would not be expected to induce a relevant harmful adverse reaction in healthy tissues.

1. **Vaccination:** TUMAPs are dissolved and administered intradermally together with an a immunomodulator, for example Granulocyte Macrophage Colony-Stimulating Factor (GM-CSF), **Figure 2**.

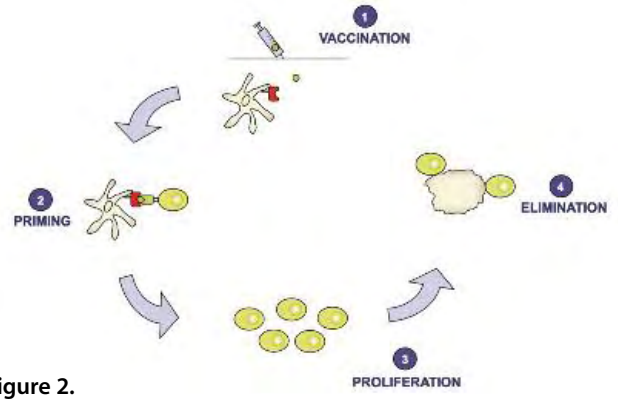

Figure 2.

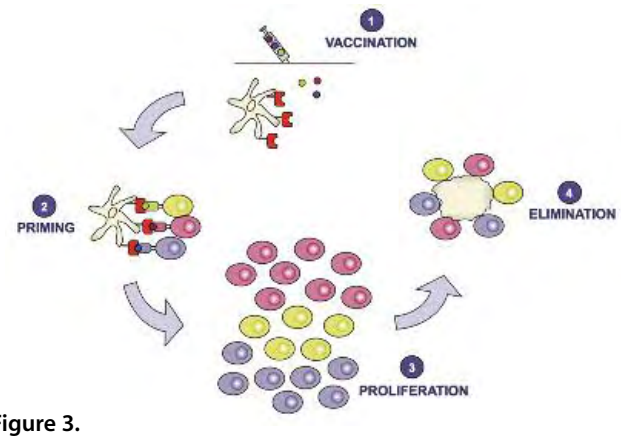

Figure 3.

2. **Priming:** TUMAPs injected into the skin encounter dermal cells (DCs). TUMAPs are then loaded directly onto surface-standing HLA molecules of the DCs at the administration site. These DCs then migrate to the lymph nodes where they encounter T cells. DCs deliver two signals to the T cells: **a.** the specific signal via the HLA-peptide complex and **b.** the co-stimulatory signal via special co-stimulatory molecules found only on the surfaces of professional antigen-presenting cells (such as DCs).

   The combination of both signals is known as "priming" and is necessary for activating previously inactive, naïve T cells, turning them into activated cytotoxic T cells.
3. **Proliferation:** Once CTLs are primed by DCs, they start to grow rapidly in number (clonal proliferation). Soon thereafter they leave the lymph nodes and blood vessels in search of cells displaying exactly the same HLA-peptide combination they were shown before on DCs in the process of priming. CTLs activated by TUMAP vaccination will seek out only cells presenting the TUMAPs (ie, tumor cells.
4. **Elimination:** Once CTLs recognize the exact HLA-peptide combination again (now on the tumor cell), they eliminate the tumor cell by releasing cytolytic substances and/or by issuing an apoptotic death signal to the tumor cell.

   However, priming of only one kind of CTL is usually insufficient to eliminate all tumor cells. Tumors are very mutagenic and are thus able to respond rapidly to CTL attacks by changing their pattern of expressed proteins, allowing them to escape from recognition by CTLs. In order to counter this tumor escape mechanism, researchers are developing products combining multiple TUMAPs (8-12 TUMAPs) which are given to the patient in a single injectable dose. In this way, a wide variety of different CTLs is primed, and CTLs can simultaneously attack the tumor at multiple target sites (**Figure 3**).

Introducing IMA901

Drug discovery technologies at Immatics Biotech-nologies, a biotechnology firm emerged from the University in Tübingen in Germany, are able to identify HLA-binding TUMAPs with highest sensitivity directly from primary human tumor tissue samples. From thousands of identified TUMAPs the most suitable ones are selected and combined to a single multi-peptide product to form a therapeutic cancer vaccine. "Suitable" required that each of such antigens are expressed in at least 60-80% of tumor tissues, overexpressed on cancer vs healthy tissue, derived from functionally relevant proteins involved in the promotion of cancer generation and growth and proven to be immunogenic in vitro. The goal is to provoke a number of specific T-cell responses which finally result in the destruction of tumor cells presenting the applied TUMAPs. IMA 901 consists of 10 synthetic tumor-associated peptides (TUMAPs) which have been identified by isolating HLA-peptide complexes from more than 30 primary human RCC specimens and determining the peptide sequences by mass spectrometry.

The Phase I IMA901 Study

First safety and efficacy data were derived from a Phase 1 study of the vaccine, and provided the impetus for further clinical development.

In that Phase I study:[26]

- IMA901 was shown to be safe and well tolerated in 28 patients with advanced RCC
- A vaccine-induced immune response was reported in 74% of patients
- Multiple vaccine-induced responses were observed in 30% of patients
- Multiple vaccine-induced responses were associated with disease control (partial response and stable disease, according to RECIST criteria (P=0.015).
- Multiple vaccine-induced responses were observed more frequently in patients with low levels of regulatory T cells prior to vaccination (P=0.016).

The Phase II IMA901 Study

The phase II study was carried out at 23 centers in 10 European countries.[27] The study recruited 68 patients with advanced/metastatic renal cell carcinoma who had failed previous first line therapy (either tyrosine kinase

inhibitors (TKI) or cytokines). Patients in the study were randomized to receive one single infusion of cyclophosphamide (CY) as immunomodulator prior to the first vaccination with the multi-peptide vaccine IMA901. CY was introduced to evaluate the impact as an additional immunomodulator as it had been observed that patients with lower regulatory T cells had a better outcome in the IMA901 phase I study.[27] The study investigated non-progression at 6 months, progression-free survival, over-all survival, correlation of immune response with clinical benefit, and safety and tolerability. Patients in the study were stratified for risk group and previous treatment and randomized to receive one single infusion of cyclophosphamide (CY; 300mg/m2) prior to the first vaccination with IMA901. Both groups of patients then received up to 17 injections of IMA901 plus GM-CSF (both intradermally) over a period of up to 9 months.

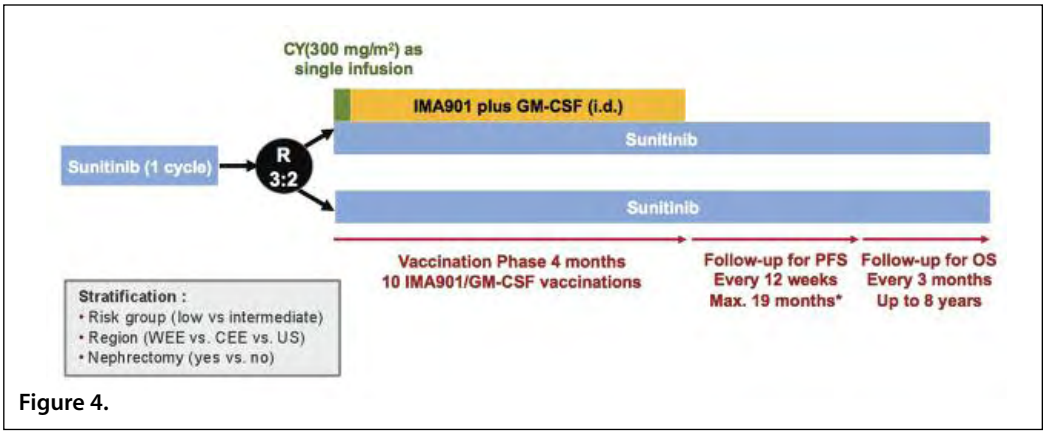

Figure 4.

Design of a Phase 3 trial evaluating the use of sunitinib in combination with vaccination to determine whether this regimen can enhance the immunologic response to IMA901.

Patients randomized to receive a single dose of CY showed a strong trend towards improved overall survival versus patients who did not receive CY (*P*=0.086; median OS not reached after 23 months of follow-up in the CY-pretreated patients versus median OS of 16 months in the other patients). The relevance of this finding was further supported by data showing that CY – as prospectively hypothesized – significantly reduced regulatory T cells (Tregs), an immune cell population thought to inhibit TUMAP-specific immune responses. Finally, patients who were able to mount a vaccine-induced immune response against tumor-derived peptides contained in IMA901, showed significantly longer survival compared to those who did not (*P*=0.048 in all patients and *P*=0.006 in CY-pretreated patients). The favorable safety profile observed in the previous phase I study was confirmed with most drug-related adverse events being mild local site reactions.

Updated Phase 2 results were presented at the European Society of Medical Oncology (ESMO) in 2010. Median survival in IMA901-202 is 19.8 months in all second-line patients previously treated with cytokines and had not been reached after >26 months follow-up in patients pretreated with CY. This compares to published results in comparable patients with a median OS of 17.8 months for sorafenib[28] and 16.4 months for sunitinib.[29] In summary, both the clinical and the immunological data received from this trial support the notion of an active therapeutic multi-peptide cancer vaccine.

IMPRINT Pivotal Phase 3 Study Vaccinates First Patients

IMPRINT is a global multicenter, randomized, controlled study in patients with metastatic and/or locally advanced RCC who are candidates for receiving standard first-line therapy with sunitinib (Sutent®,Pfizer). The trial will include approximately 330 patients across the US and Europe

The primary endpoint of the Phase III study is overall survival in patients receiving IMA901 in combination with sunitinib versus sunitinib alone.[30] Overall survival will also be tested in patients who are positive for a prospectively defined biomarker signature. This signature was identified as being predictive for improved clinical outcome in IMA901-vaccinated patients in the previous Phase II study. Details on the biomarker consisting of the serum proteins Apolipoprotein A1 and CCL17 were presented in the plenary session of the Annual Meeting of Association for Cancer Immunotherapy (CIMT) in late May 2011.[31] If one or both markers are found extensively in the serum of RCC patients, such patients were shown to have better immune response and survival in the Phase II study. Further secondary endpoints include progression-free survival, safety and tolerability, and cellular immunomonitoring to assess the T-cell response to the peptides contained in IMA901.

Sunitinib as immunomodulator

Various reports have indicated that sunitinib, besides its direct effects on tumor cells, may exert immunomodulatory effects. Myeloid-derived suppressor cells (MDSC) are decreased after 1 cycle of sunitinib.[32] Furthermore, it has been shown in the IMA901 phase 2 trial that patients pretreated with sunitinib have a lower frequency of regulatory T cells . In consequence, pre-treatment with sunitinib may positively enhance immune responses to therapeutic vaccination. The mechanism underlying the use of sunitinib appears to be in contrast to the activity of sorafenib. This tyrosine kinase receptor inhibitor did not produce the same effect on T cells as sunitinib.[33]

To analyze the effects of both TKIs on cytotoxic T-cell induction in vivo, C57BL/6 mice were pretreated with sorafenib or sunitinib and immunized with $OVA_{257-264}$ peptide. In a mouse model, sorafenib, but not sunitinib,

(continued on page 115)

In Advanced Renal Cell Carcinoma...

Indication

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

Important Safety Information

WARNING: HEPATOTOXICITY
Severe and fatal hepatotoxicity has been observed in clinical studies. Monitor hepatic function and interrupt, reduce, or discontinue dosing as recommended. See "Warnings and Precautions,"Section 5.1, in complete Prescribing Information.

Hepatic Effects: Patients with pre-existing hepatic impairment should use VOTRIENT with caution. Treatment with VOTRIENT is not recommended in patients with severe hepatic impairment. Increases in serum transaminase levels (ALT, AST) and bilirubin were observed. Severe and fatal hepatotoxicity has occurred. Transaminase elevations occur early in the course of treatment (92.5% of all transaminase elevations of any grade occurred in the first 18 weeks). Before the initiation of treatment and regularly during treatment, **monitor hepatic function and interrupt, reduce, or discontinue dosing as recommended**.

QT Prolongation and Torsades de Pointes: Prolonged QT intervals and arrhythmias, including torsades de pointes, have been observed with VOTRIENT. Use with caution in patients at higher risk of developing QT interval prolongation, in patients taking antiarrhythmics or other medications that may prolong QT interval, and those with relevant pre-existing cardiac disease. Baseline and periodic monitoring of electrocardiograms and maintenance of electrolytes within the normal range should be performed.

Hemorrhagic Events: Fatal hemorrhagic events have been reported (all grades [16%] and Grades 3 to 5 [2%]). VOTRIENT has not been studied in patients who have a history of hemoptysis, cerebral, or clinically significant gastrointestinal hemorrhage in the past 6 months and should not be used in those patients.

Arterial Thrombotic Events: Arterial thrombotic events have been observed and can be fatal. In clinical RCC studies of VOTRIENT, myocardial infarction, angina, ischemic stroke, and transient ischemic attack (all grades [3%] and Grades 3 to 5 [2%]) were observed. Use with caution in patients who are at increased risk for these events.

Gastrointestinal Perforation and Fistula: Gastrointestinal perforation or fistula has occurred. Fatal perforation events have occurred. Use with caution in patients at risk for gastrointestinal perforation or fistula. Monitor for symptoms of gastrointestinal perforation or fistula.

Hypertension: Hypertension has been observed. Hypertension was observed in 47% of patients with RCC treated with VOTRIENT. Hypertension occurs early in the course of treatment (88% occurred in the first 18 weeks). Blood pressure should be well-controlled prior to initiating VOTRIENT. Monitor for hypertension and treat as needed. If hypertension persists despite antihypertensive therapy, the dose of VOTRIENT may be reduced or discontinued as appropriate.

Move Forward With VOTRIENT

In a phase 3, randomized, double-blind, placebo-controlled trial, VOTRIENT provided significant improvement in progression-free survival (PFS) in both treatment-naïve and cytokine-pretreated patients with advanced RCC[1,2]

All patients
9.2 months
(95% CI, 7.4-12.9)
overall median PFS with VOTRIENT (n=290) vs **4.2 months** (95% CI, 2.8-4.2) with placebo (n=145) (P<0.001)[2,3]

Treatment-naïve patients
11.1 months
(95% CI, 7.4-14.8)
median PFS with VOTRIENT (n=155) vs **2.8 months** (95% CI, 1.9-5.6) with placebo (n=78) (P<0.001)[2,3]

Cytokine-pretreated patients
7.4 months
(95% CI, 5.6-12.9)
median PFS with VOTRIENT (n=135) vs **4.2 months** (95% CI, 2.8-5.6) with placebo (n=67) (P<0.001)[2,3]

NCCN Guidelines Category 1 recommendation[4]

- First-line therapy for relapsed or Stage IV unresectable RCC of predominant clear cell histology

Proven safety profile[1,2]

- Most common adverse events observed with VOTRIENT (>20%) were diarrhea, hypertension, hair color changes (depigmentation), nausea, anorexia, and vomiting
  - — Grade 3/4 fatigue occurred in 2% of patients; all grades, 19%
  - — Grade 3/4 asthenia occurred in 3% of patients; all grades, 14%

Most common laboratory abnormalities were ALT and AST increases[1]

- Grade 3 ALT increases occurred in 10% of patients; grade 4, 2%
- In clinical trials, 92.5% of all transaminase elevations of any grade occurred in the first 18 weeks of treatment with VOTRIENT
- Monitor serum liver tests before initiation of treatment with VOTRIENT and at least once every 4 weeks for at least the first 4 months of treatment or as clinically indicated. Periodic monitoring should then continue after this time period

Once-daily oral dosing[1]

- The recommended dosage of VOTRIENT is 800 mg once daily without food (at least 1 hour before or 2 hours after a meal)
- Dose modifications, interruptions, and discontinuations may be required in patients with hepatic impairment, drug interactions, and following adverse events
- Forty-two percent of patients on VOTRIENT required a dose interruption; 36% of patients on VOTRIENT were dose-reduced

VOTRIENT is a multitargeted tyrosine kinase inhibitor that is indicated for the treatment of patients with advanced RCC.

Votrient™
pazopanib tablets (200 mg)

Wound Healing: VOTRIENT may impair wound healing. Temporary interruption of therapy with VOTRIENT is recommended in patients undergoing surgical procedures. VOTRIENT should be discontinued in patients with wound dehiscence.

Hypothyroidism: Hypothyroidism was reported as an adverse reaction in 26/586 (4%). Monitoring of thyroid function tests is recommended.

Proteinuria: Monitor urine protein. Proteinuria was reported in 44/586 (8%) (Grade 3, 5/586 [<1%] and Grade 4, 1/586 [<1%]). Baseline and periodic urinalysis during treatment is recommended. Discontinue for Grade 4 proteinuria.

Pregnancy Category D: VOTRIENT can cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant while taking VOTRIENT.

Drug Interactions: CYP3A4 Inhibitors (eg, ketoconazole, ritonavir, clarithromycin): Avoid use of strong inhibitors. Consider dose reduction of VOTRIENT when administered with strong CYP3A4 inhibitors.

CYP3A4 Inducers (such as rifampin): Consider an alternate concomitant medication with no or minimal enzyme induction potential or avoid VOTRIENT.

CYP Substrates: Concomitant use of VOTRIENT with agents with narrow therapeutic windows that are metabolized by CYP3A4, CYP2D6, or CYP2C8 is not recommended.

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

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

VOTRIENT has been associated with cardiac dysfunction (such as a decrease in ejection fraction and congestive heart failure) in patients with various cancer types, including RCC. In the overall safety population for RCC (N=586), cardiac dysfunction was observed in 4/586 patients (<1%).

Please see Brief Summary of Prescribing Information on adjacent pages.

References: 1. VOTRIENT Prescribing Information. Research Triangle Park, NC: GlaxoSmith-Kline; 2010. **2.** Sternberg CN, et al. *J Clin Oncol.* 2010;28(6):1061–1068. **3.** Data on file, GlaxoSmithKline. **4.** Referenced with permission from ©National Comprehensive Cancer Network, Inc 2010. All Rights Reserved. NCCN Guidelines™: Kidney Cancer, V.1.2011. NCCN.org Accessed January 12, 2011. NCCN® and NCCN GUIDELINES™ are trademarks owned by the National Comprehensive Cancer Network, Inc.

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gsk GlaxoSmithKline
Oncology

BRIEF SUMMARY

VOTRIENT™ (pazopanib) tablets

The following is a brief summary only; see full prescribing information for complete product information.

WARNING: HEPATOTOXICITY

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

1 INDICATIONS AND USAGE

VOTRIENT™ is indicated for the treatment of patients with advanced renal cell carcinoma (RCC).

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing: The recommended dose of VOTRIENT is 800 mg orally once daily without food (at least 1 hour before or 2 hours after a meal) *[see Clinical Pharmacology (12.3) of full prescribing information]*. The dose of VOTRIENT should not exceed 800 mg. Do not crush tablets due to the potential for increased rate of absorption which may affect systemic exposure. *[See Clinical Pharmacology (12.3) of full prescribing information*.] If a dose is missed, it should not be taken if it is less than 12 hours until the next dose. **2.2 Dose Modification Guidelines:** Initial dose reduction should be 400 mg, and additional dose decrease or increase should be in 200 mg steps based on individual tolerability. The dose of VOTRIENT should not exceed 800 mg. Hepatic Impairment: The dosage of VOTRIENT in patients with moderate hepatic impairment should be reduced to 200 mg per day. There are no data in patients with severe hepatic impairment; therefore, use of VOTRIENT is not recommended in these patients. *[See Use in Specific Populations (8.6).]* Concomitant Strong CYP3A4 Inhibitors: The concomitant use of strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir, clarithromycin) may increase pazopanib concentrations and should be avoided. If coadministration of a strong CYP3A4 inhibitor is warranted, reduce the dose of VOTRIENT to 400 mg. Further dose reductions may be needed if adverse effects occur during therapy. This dose is predicted to adjust the pazopanib AUC to the range observed without inhibitors. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inhibitors. *[See Drug Interactions (7.1).]* Concomitant Strong CYP3A4 Inducer: The concomitant use of strong CYP3A4 inducers (e.g., rifampin) may decrease pazopanib concentrations and should be avoided. VOTRIENT should not be used in patients who can not avoid chronic use of strong CYP3A4 inducers. *[See Drug Interactions (7.1).]*

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hepatic Effects: In clinical trials with VOTRIENT, hepatotoxicity, manifested as increases in serum transaminases (ALT, AST) and bilirubin, was observed *[see Adverse Reactions (6.1)]*. This hepatotoxicity can be severe and fatal. Transaminase elevations occur early in the course of treatment (92.5% of all transaminase elevations of any grade occurred in the first 18 weeks). Across all monotherapy studies with VOTRIENT, ALT >3 X upper limit of normal (ULN) was reported in 138/977 (14%) and ALT >8 X ULN was reported in 40/977 (4%) of patients who received VOTRIENT. Concurrent elevations in ALT >3 X ULN and bilirubin >2 X ULN regardless of alkaline phosphatase levels were detected in 13/977 (1%) of patients. Four of the 13 patients had no other explanation for these elevations. Two of 977 (0.2%) patients died with disease progression and hepatic failure. Monitor serum liver tests before initiation of treatment with VOTRIENT and at least once every 4 weeks for at least the first 4 months of treatment or as clinically indicated. Periodic monitoring should then continue after this time period. Patients with isolated ALT elevations between 3 X ULN and 8 X ULN may be continued on VOTRIENT with weekly monitoring of liver function until ALT return to Grade 1 or baseline. Patients with isolated ALT elevations of >8 X ULN should have VOTRIENT interrupted until they return to Grade 1 or baseline. If the potential benefit for reinitiating treatment with VOTRIENT is considered to outweigh the risk for hepatotoxicity, then reintroduce VOTRIENT at a reduced dose of no more than 400 mg once daily and measure serum liver tests weekly for 8 weeks *[see Dosage and Administration (2.2)]*. Following reintroduction of VOTRIENT, if ALT elevations >3 X ULN recur, then VOTRIENT should be permanently discontinued. If ALT elevations >3 X ULN occur concurrently with bilirubin elevations >2 X ULN, VOTRIENT should be permanently discontinued. Patients should be monitored until resolution. VOTRIENT is a UGT1A1 inhibitor. Mild, indirect (unconjugated) hyperbilirubinemia may occur in patients with Gilbert's syndrome *[see Clinical Pharmacology (12.5) of full prescribing information]*. Patients with only a mild indirect hyperbilirubinemia, known Gilbert's syndrome, and elevation in ALT >3 X ULN should be managed as per the recommendations outlined for isolated ALT elevations. The safety of VOTRIENT in patients with pre-existing severe hepatic impairment, defined as total bilirubin >3 X ULN with any level of ALT, is unknown. Treatment with VOTRIENT is not recommended in patients with severe hepatic impairment. *[See Dosage and Administration (2.2) and Use in Specific Populations (8.6).]*

5.2 QT Prolongation and Torsades de Pointes: In clinical RCC studies of VOTRIENT, QT prolongation (≥500 msec) was identified on routine electrocardiogram monitoring in 11/558 (<2%) of patients. Torsades de pointes occurred in 2/977 (<1%) of patients who received VOTRIENT in the monotherapy studies. In the randomized clinical trial, 3 of the 290 patients receiving VOTRIENT had post-baseline values between 500 to 549 msec. None of the 145 patients receiving placebo had post-baseline QTc values ≥500 msec. VOTRIENT should be used with caution in patients with a history of QT interval prolongation, in patients taking antiarrhythmics or other medications that may prolong QT interval, and those with relevant pre-existing cardiac disease. When using VOTRIENT, baseline and periodic monitoring of electrocardiograms and maintenance of electrolytes (e.g., calcium, magnesium, potassium) within the normal range should be performed. **5.3 Hemorrhagic Events:** In clinical RCC studies of VOTRIENT, hemorrhagic events have been reported [all Grades (16%) and Grades 3 to 5 (2%)]. Fatal hemorrhage has occurred in 5/586 (0.9%) *[see Adverse Reactions (6.1)]*. VOTRIENT has not been studied in patients who have a history of hemoptysis, cerebral, or clinically significant gastrointestinal hemorrhage in the past 6 months and should not be used in those patients. **5.4 Arterial Thrombotic Events:** In clinical RCC studies of VOTRIENT, myocardial infarction, angina, ischemic stroke, and transient ischemic attack [all Grades (3%) and Grades 3 to 5 (2%)] were observed. Fatal events have been observed in 2/586 (0.3%). In the randomized study, these events were observed more frequently with VOTRIENT compared to placebo *[see Adverse Reactions (6.1)]*. VOTRIENT should be used with caution in patients who are at increased risk for these events or who have had a history of these events. VOTRIENT has not been studied in patients who have had an event within the previous 6 months and should not be used in those patients. **5.5 Gastrointestinal Perforation and Fistula:** In clinical RCC studies of VOTRIENT, gastrointestinal perforation or fistula has been reported in 5 patients (0.9%). Fatal perforation events have occurred in 2/586 (0.3%). Monitor for symptoms of gastrointestinal perforation or fistula. **5.6 Hypertension:** Blood pressure should be well-controlled prior to initiating VOTRIENT. Patients should be monitored for hypertension and treated as needed with anti-hypertensive therapy. Hypertension (systolic blood pressure ≥150 or diastolic blood pressure ≥100 mm Hg) was observed in 47% of patients with RCC treated with VOTRIENT. Hypertension occurs early in the course of treatment (88% occurred in the first 18 weeks). *[See Adverse Reactions (6.1).]* In the case of persistent hypertension despite anti-hypertensive therapy, the dose of VOTRIENT may be reduced *[see Dosage and Administration (2.2)]*. VOTRIENT should be discontinued if hypertension is severe and persistent despite anti-hypertensive therapy and dose reduction of VOTRIENT. **5.7 Wound Healing:** No formal studies on the effect of VOTRIENT on wound healing have been conducted. Since vascular endothelial growth factor receptor (VEGFR) inhibitors such as pazopanib may impair wound healing, treatment with VOTRIENT should be stopped at least 7 days prior to scheduled surgery. The decision to resume VOTRIENT after surgery should be based on clinical judgment of adequate wound healing. VOTRIENT should be discontinued in patients with wound dehiscence. **5.8 Hypothyroidism:** In clinical RCC studies of VOTRIENT, hypothyroidism reported as an adverse reaction in 26/586 (4%) *[see Adverse Reactions (6.1)]*. Proactive monitoring of thyroid function tests is recommended. **5.9 Proteinuria:** In clinical RCC studies with VOTRIENT, proteinuria has been reported in 44/586 (8%) [Grade 3, 5/586 (<1%) and Grade 4, 1/586 (<1%)] *[see Adverse Reactions (6.1)]*. Baseline and periodic urinalysis during treatment is recommended. VOTRIENT should be discontinued if the patient develops Grade 4 proteinuria. **5.10 Pregnancy:** VOTRIENT can cause fetal harm when administered to a pregnant woman. Based on its mechanism of action, VOTRIENT is expected to result in adverse reproductive effects. In pre-clinical studies in rats and rabbits, pazopanib was teratogenic, embryotoxic, fetotoxic, and abortifacient. There are no adequate and well-controlled studies of VOTRIENT in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while taking VOTRIENT. *[See Use in Specific Populations (8.1).]*

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of VOTRIENT has been evaluated in 977 patients in the monotherapy studies which included 586 patients with RCC. With a median duration of treatment of 7.4 months (range 0.1 to 27.6), the most commonly observed adverse reactions (≥20%) in the 586 patients were diarrhea, hypertension, hair color change, nausea, fatigue, anorexia, and vomiting. The data described below reflect the safety profile of VOTRIENT in 290 RCC patients who participated in a randomized, double-blind, placebo-controlled study *[see Clinical Studies (14) of full prescribing information]*. The median duration of treatment was 7.4 months (range 0 to 23) for patients who received VOTRIENT and 3.8 months (range 0 to 22) for the placebo arm. Forty-two percent (42%) of patients on VOTRIENT required a dose interruption. Thirty-six percent (36%) of patients on VOTRIENT were dose reduced.

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

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

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

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

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

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

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

Hepatic Toxicity: In a controlled clinical study with VOTRIENT for the treatment of RCC, ALT >3 X ULN was reported in 18% and 3% of the VOTRIENT and placebo groups, respectively. ALT >10 X ULN was reported in 4% of patients who received VOTRIENT and in <1% of patients who received placebo. Concurrent elevation in ALT >3 X ULN and bilirubin >2 X ULN in the absence of significant alkaline phosphatase >3 X ULN occurred in 5/290 (2%) of patients on VOTRIENT and 2/145 (1%) on placebo. *[See Dosage and Administration (2.2) and Warnings and Precautions (5.1).]*
Hypertension: In a controlled clinical study with VOTRIENT for the treatment of RCC, 115/290 patients (40%) receiving VOTRIENT compared with 15/145 patients (10%) on placebo experienced hypertension. Grade 3 hypertension was reported in 13/290 patients (4%) receiving VOTRIENT compared with 1/145 patients (<1%) on placebo. The majority of cases of hypertension were manageable with anti-hypertensive agents or dose reductions with 2/290 patients (<1%) permanently discontinuing treatment with VOTRIENT because of hypertension. In the overall safety population for RCC (N = 586), one patient had hypertensive crisis on VOTRIENT. [*See Warnings and Precautions (5.2).*] QT Prolongation and Torsades de Pointes: In a controlled clinical study with VOTRIENT, QT prolongation (≥500 msec) was identified on routine electrocardiogram monitoring in 3/290 (1%) of patients treated with VOTRIENT compared with no patients on placebo. Torsades de pointes was reported in 2/586 (<1%) patients treated with VOTRIENT in the RCC studies. *[See Warnings and Precautions (5.3).]* Arterial Thrombotic Events: In a controlled clinical study with VOTRIENT, the incidences of arterial thrombotic events such as myocardial infarction/ischemia [5/290 (2%)], cerebral vascular accident [1/290 (<1%)], and transient ischemic attack [4/290 (1%)] were higher in patients treated with VOTRIENT compared to the placebo arm (0/145 for each event). *[See Warnings and Precautions (5.4).]* Hemorrhagic Events: In a controlled clinical study with VOTRIENT, 37/290 patients (13%) treated with VOTRIENT and 7/145 patients (5%) on placebo experienced at least 1 hemorrhagic event. The most common hemorrhagic events in the patients treated with VOTRIENT were hematuria (4%), epistaxis (2%), hemoptysis (2%), and rectal hemorrhage (1%). Nine (9/37) patients treated with VOTRIENT who had hemorrhagic events experienced serious events including pulmonary, gastrointestinal, and genitourinary hemorrhage. Four (4/290) (1%) patients treated with VOTRIENT died from hemorrhage compared with no (0/145) (0%) patients on placebo. *[See Warnings and Precautions (5.5).]* In the overall safety population in RCC (N = 586), cerebral/intracranial hemorrhage was observed in 2/586 (<1%) patients treated with VOTRIENT. Hypothyroidism: In a controlled clinical study with VOTRIENT, more patients had a shift from thyroid stimulating hormone (TSH) within the normal range at baseline to above the normal range at any post-baseline visit in VOTRIENT compared with the placebo arm (27% compared with 5%, respectively). Hypothyroidism was reported as an adverse reaction in 19 patients (7%) treated with VOTRIENT and no patients (0%) in the placebo arm. *[See Warnings and Precautions (5.7).]* Diarrhea: Diarrhea occurred frequently and was predominantly mild to moderate in severity. Patients should be advised how to manage mild diarrhea and to notify their healthcare provider if moderate to severe diarrhea occurs so appropriate management can be implemented to minimize its impact. Proteinuria: In the controlled clinical study with VOTRIENT, proteinuria has been reported as an adverse reaction in 27 patients (9%) treated with VOTRIENT. In 2 patients, proteinuria led to discontinuation of treatment with VOTRIENT. Lipase Elevations: In a single-arm clinical study, increases in lipase values were observed for 48/181 patients (27%). Elevations in lipase as an adverse reaction were reported for 10 patients (4%) and were Grade 3 for 6 patients and Grade 4 for 1 patient. In clinical RCC studies of VOTRIENT, clinical pancreatitis was observed in 4/586 patients (<1%). Cardiac Dysfunction: Pazopanib has been associated with cardiac dysfunction (such as a decrease in ejection fraction and congestive heart failure) in patients with various cancer types, including RCC. In the overall safety population for RCC (N = 586), cardiac dysfunction was observed in 4/586 patients (<1%).

7 DRUG INTERACTIONS

7.1 Drugs That Inhibit or Induce Cytochrome P450 3A4 Enzymes: In vitro studies suggested that the oxidative metabolism of pazopanib in human liver microsomes is mediated primarily by CYP3A4, with minor contributions from CYP1A2 and CYP2C8. Therefore, inhibitors and inducers of CYP3A4 may alter the metabolism of pazopanib. CYP3A4 Inhibitors: Coadministration of pazopanib with strong inhibitors of CYP3A4 (e.g., ketoconazole, ritonavir, clarithromycin) may increase pazopanib concentrations. A dose reduction for VOTRIENT should be considered when it must be coadministered with strong CYP3A4 inhibitors *[see Dosage and Administration (2.2)]*. Grapefruit juice should be avoided as it inhibits CYP3A4 activity and may also increase plasma concentrations of pazopanib. CYP3A4 Inducers: CYP3A4 inducers such as rifampin may decrease plasma pazopanib concentrations. VOTRIENT should not be used if chronic use of strong CYP3A4 inducers can not be avoided *[see Dosage and Administration (2.2)]*. **7.2 Effects of Pazopanib on CYP Substrates:** Results from drug-drug interaction studies conducted in cancer patients suggest that pazopanib is a weak inhibitor of CYP3A4, CYP2C8, and CYP2D6 in vivo, but had no effect on CYP1A2, CYP2C9, or CYP2C19 *[see Clinical Pharmacology (12.3) of full prescribing information]*. Concomitant use of VOTRIENT with agents with narrow therapeutic windows that are metabolized by CYP3A4, CYP2D6, or CYP2C8 is not recommended. Coadministration may result in inhibition of the metabolism of these products and create the potential for serious adverse events. *[See Clinical Pharmacology (12.3) of full prescribing information.]*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy: Pregnancy Category D *[see Warnings and Precautions (5.10)]*. VOTRIENT can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of VOTRIENT in pregnant women. In pre-clinical studies in rats and rabbits, pazopanib was teratogenic, embryotoxic, fetotoxic, and abortifacient. Administration of pazopanib to pregnant rats during organogenesis at a dose level of ≥3 mg/kg/day (approximately 0.1 times the human clinical exposure based on AUC) resulted in teratogenic effects including cardiovascular malformations (retroesophageal subclavian artery, missing innominate artery, changes in the aortic arch) and incomplete or absent ossification. In addition, there was

reduced fetal body weight, and pre- and post-implantation embryolethality in rats administered pazopanib at doses ≥3 mg/kg/day. In rabbits, maternal toxicity (reduced food consumption, increased post-implantation loss, and abortion) was observed at doses ≥30 mg/kg/day (approximately 0.007 times the human clinical exposure). In addition, severe maternal body weight loss and 100% litter loss were observed at doses ≥100 mg/kg/day (0.02 times the human clinical exposure), while fetal weight was reduced at doses ≥3 mg/kg/day (AUC not calculated). **8.3 Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from VOTRIENT, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **8.4 Pediatric Use:** The safety and effectiveness of VOTRIENT in pediatric patients have not been established. In repeat-dose toxicology studies in rats including 4-week, 13-week, and 26-week administration, toxicities in bone, teeth, and nail beds were observed at doses ≥3 mg/kg/day (approximately 0.07 times the human clinical exposure based on AUC). Doses of 300 mg/kg/day (approximately 0.8 times the human clinical exposure based on AUC) were not tolerated in 13- and 26-week studies with rats. Body weight loss and morbidity were observed at these doses. Hypertrophy of epiphyseal growth plates, nail abnormalities (including broken, overgrown, or absent nails) and tooth abnormalities in growing incisor teeth (including excessively long, brittle, broken and missing teeth, and dentine and enamel degeneration and thinning) were observed in rats at ≥30 mg/kg/day (approximately 0.35 times the human clinical exposure based on AUC) at 26 weeks, with the onset of tooth and nail bed alterations noted clinically after 4 to 6 weeks. **8.5 Geriatric Use:** In clinical trials with VOTRIENT for the treatment of RCC, 196 subjects (33%) were aged ≥65 years, and 34 subjects (6%) were aged >75 years. No overall differences in safety or effectiveness of VOTRIENT were observed between these subjects and younger subjects. However, patients >60 years of age may be at greater risk for an ALT >3 X ULN. Other reported clinical experience has not identified differences in responses between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. **8.6 Hepatic Impairment:** The safety and pharmacokinetics of pazopanib in patients with hepatic impairment have not been fully established. In clinical studies for VOTRIENT, patients with total bilirubin ≤1.5 X ULN and AST and ALT ≤2 X ULN were included *[see Warnings and Precautions (5.1)]*. An interim analysis of data from 12 patients with normal hepatic function and 9 with moderate hepatic impairment showed that the maximum tolerated dose in patients with moderate hepatic impairment was 200 mg per day *[see Clinical Pharmacology (12.3) of full prescribing information]*. There are no data on patients with severe hepatic impairment *[see Dosage and Administration (2.2)]*. **8.7 Renal Impairment:** Patients with renal cell cancer and mild/moderate renal impairment (creatinine clearance ≥30 mL/min) were included in clinical studies for VOTRIENT. There are no clinical or pharmacokinetic data in patients with severe renal impairment or in patients undergoing peritoneal dialysis or hemodialysis. However, renal impairment is unlikely to significantly affect the pharmacokinetics of pazopanib since <4% of a radiolabeled oral dose was recovered in the urine. In a population pharmacokinetic analysis using 408 subjects with various cancers, creatinine clearance (30-150 mL/min) did not influence clearance of pazopanib. Therefore, renal impairment is not expected to influence pazopanib exposure, and dose adjustment is not necessary.

10 OVERDOSAGE

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

13 NONCLINICAL TOXICOLOGY

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

17 PATIENT COUNSELING INFORMATION

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

- Therapy with VOTRIENT may result in hepatobiliary laboratory abnormalities. Monitor serum liver tests (ALT, AST, and bilirubin) prior to initiation of VOTRIENT and at least once every 4 weeks for the first 4 months of treatment or as clinically indicated. Inform patients that they should report any of the following signs and symptoms of liver problems to their healthcare provider right away.
  - yellowing of the skin or the whites of the eyes (jaundice),
  - unusual darkening of the urine,
  - unusual tiredness,
  - right upper stomach area pain.
- Gastrointestinal adverse reactions such as diarrhea, nausea, and vomiting have been reported with VOTRIENT. Patients should be advised how to manage diarrhea and to notify their healthcare provider if moderate to severe diarrhea occurs.
- Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant.
- Patients should be advised to inform their healthcare providers of all concomitant medications, vitamins, or dietary and herbal supplements.
- Patients should be advised that depigmentation of the hair or skin may occur during treatment with VOTRIENT.
- Patients should be advised to take VOTRIENT without food (at least 1 hour before or 2 hours after a meal).

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application significantly reduced the induction of antigen-specific T cells. Numbers of regulatory T cells were reduced in peripheral blood mononuclear cells from mice treated with sunitinib. These results indicate that sunitinib, but not sorafenib, could be suitable for combination with immunotherapeutic approaches for treatment of cancer patients. In addition, disease control with sunitinib may be required to allow time for a given patient to develop an anti-tumor immune response. It is possible that previous immunotherapy would have had a greater effect but progressive disease limiting a patient's lifespan precluded this.

In order to allow for a reduction of regulatory T cells and not to compromise any initial T cell proliferation, a trial design was chosen in which patients start on 1 cycle of sunitinib (4/2 schedule); following the first 4 weeks of sunitinib treatment, patients will then be randomized and the first 4 vaccinations will be administered before the second cycle of sunitinib commences (see **Figure 4**).

Current timelines for the IMPRINT trial anticipate the last patient to be enrolled in IMPRINT until the end of 2012. First data (progression-free survival, immune responses, first analysis of overall survival) are estimated to be available by early 2014.

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Two Researchers Offer Insights on the Ground-Breaking Discovery and Pivotal Trial of a New Multipeptide Vaccine

Harpreet Singh, PhD, and Carsten Reinhardt, MD, PhD, head a team of physicians, biochemists and immunologists at immatics biotechnologies, Gmbh, based in Tuebingen, Germany. The company has developed peptide-based active immunotherapy for various cancers. The company's most advanced product is currently in a phase 3 clinical trial for kidney cancer. This interview was conducted by Robert A. Figlin, MD, Editor-in-Chief of the Kidney Cancer Journal.

Dr. Figlin: Please introduce yourselves and tell us the role you play in this research effort.

Dr Singh: I am co-founder and Chief Scientific Officer at immatics. I have always been fascinated by the immune system. After studying biochemistry at the University of Tuebingen (Germany), I joined the immunology research group of Hans-Georg Rammensee, a pioneer in the field of molecular immunology who discovered how antigens are presented to the immune system by peptides bound to Major Histocompatibility Complex (MHC, called HLA in humans). Driven by the wish to translate our findings into the clinical setting, we founded the company 10 years ago. Meanwhile we have conducted or are conducting a number of clinical studies ranging from phase 1 to 3 in renal cell cancer, colorectal cancer and glioma. Our mission and our passion are to perform *science-driven* clinical development and maintaining this even up to phase 3 studies.

Dr Reinhardt: I joined immatics in October 2009 as Chief Medical Officer just a few months before the company received the exciting data from the randomized IMA901 phase 2 study which eventually led to the IMPRINT phase 3 trial. My key responsibilities comprise all areas of clinical development and primarily include designing clinical trial programs relevant for both patients and regulatory authorities. This not only a process of putting together and integrating all available knowledge about the specific compound under development but largely depends on the interactions with and input from key clinical experts and authorities such as FDA in the US and EMA in the European Union. Before joining immatics, I was Chief Medical Officer at Micromet Inc., a biopharmaceutical company developing highly innovative antibody formats (so-called BiTEs) for various hematology/oncology indications and was responsible for the continued development of Herceptin®, an anti-HER2 antibody for treating breast and gastric cancers, when being International Medical Leader at Roche Pharmaceuticals. I have always been extremely excited by the opportunity to contribute in the search for patient s future treatment options.

Dr. Figlin: Please describe the scientific rationale for the approach you are using in renal cell carcinoma.

Dr Reinhardt: Renal cell cancer, similar to malignant melanoma, has for a long time been known as an "immune-responsive" cancer indication and thus represented a promising first indication to develop our multipeptide therapeutic vaccines. While the various new drugs now available for the treatment of advanced RCC have made a significant impact on the course of disease, it appears that long-term benefit in terms of overall survival improvement or even cure is a goal still to be achieved. The data available for cytokine treatment in this indication, specifically long-term survivors observed after high-dose IL-2 administration, clearly indicate the promise of immunotherapy, however the side effect profile and the limited population benefiting has significantly hampered its wider use. We at immatics believe that treatment with IMA901 may, due to its highly specific mode of action, achieve the positive effects seen for unspecific immunotherapy, however without the unspecific side effects and therefore applicable for a broader patient population.

Dr Singh: An additional motivation for us to move into RCC was that before we founded the company we had conducted a small investigator-initiated trial in advanced renal cell cancer patients using two of our earliest peptides. It was the first time that we had observed an association of immune response with clinical response (according to WHO criteria) which we felt was encouraging enough to move into a setting with more and better peptides identified with our antigen discovery platform.

Dr. Figlin: Please describe the results of both laboratory and clinical data that led to this pivotal trial.

Dr Singh: One of the other founders of immatics, Toni Weinschenk, who is Head of Discovery at our company, made a breakthrough discovery in 2001: by combining various methods we were able to identify a large number of over-expressed HLA-bound peptides from a primary RCC tissue and select those that would have been appro-

priate for therapeutic purposes. This was the starting point for a large-scale analysis resulting into what we call the "renal cell cancer peptidome". From this database we selected the best antigens found abundantly and shared on RCC and designated this multi-peptide set IMA901, our first product candidate.

In the phase 1 study conducted in 28 patients we found that immune responses to IMA901 were positively associated with tumor stabilization while we found that regulatory T cells (Tregs, which are thought to inhibit our cancer-specific T cells) were negatively associated with immune responses. Based on reports that low doses of cyclophosphamide (CY) may act immuno-modulatory by decreasing numbers of Tregs, we, in the phase 2 study, introduced a single dose of CY in a randomized fashion. Indeed, in the phase 2 study in 68 patients we found that patients pre-treated with a single dose of CY showed significantly reduced numbers of Tregs, a favorable survival compared to non-CY pretreated patients and a significant association of immune response with overall survival.

Dr Reinhardt: In addition to the data just mentioned by Dr Singh, we have also looked at the clinical data in the context of expected clinical outcome in the patient populations tested in our phase 2 trial. While we have not seen a clear impact on short-term progression, the analysis of overall survival showed survival rates clearly exceeding expected levels (ie. more than 75% of cytokine-pretreated patients still alive after 18 months in the CY arm). In fact, this pattern of dissociation between short- and long-term clinical parameters is known as the "delayed effect" of immunotherapeutics and is exactly what we would have expected from an active therapeutic vaccine. These results, together with the clear association of outcome with immune response to our vaccine gave us the confidence to move forward and to start the phase 3 trial program.

Dr. Figlin: Please discuss the rationale to use the approach in combination with sunitinib.

Dr Singh: We published some initial preclinical studies in 2008 showing that sunitinib was compatible and even possibly synergistic with therapeutic vaccines while sorafenib strongly diminished the immune response when given concurrently with the vaccine. So we and also others, like Jim Finke and Brian Rini in Cleveland, further investigated the impact of sunitinib on the immune system. Jim could show that RCC patients with sunitinib did not only have reduced Tregs but also experienced a reduction of a novel class of inhibitory cells, so-called myeloid-derived suppressor cells (MDSC). We at the same time discovered that RCC patients had massively upregulated levels of MDSC and that two types of MDSC were significantly and negatively associated with survival of RCC patients. Based on all the evidence now published by several groups we believe that sunitinib is not only compatible with therapeutic vaccines but actually offers a highly interesting potential for synergistic activity in two ways: Firstly, it has an effect rather on PFS than on OS while a cancer vaccine like IMA901 we expect to have an impact primarily on overall survival. Secondly, Sunitinib (possibly in contrast to other TKIs approved in RCC) downmodulates exactly those cellular populations we have found to have the strongest negative impact on immunity in our own studies.

Dr. Figlin: Please describe the schema for the pivotal trial and where it will be conducted.

Dr Reinhardt: After having received the encouraging phase 2 data we have had many discussions with key opinion leaders including our lead investigators Brian Rini from Cleveland and Tim Eisen from Cambridge about the best way forward based on scientific data. We finally concluded that it may be best to start patients on sunitinib treatment for one cycle to reduce immunosuppressive cell populations and then start IMA901 vaccinations in the first treatment pause (ie. in the 2-week off-period of the 4/2 schedule). Patients who qualify for continued treatment after 1 cycle of sunitinib (ie. no prohibitive AE, no clinical progression) are being randomized to either continued sunitinib or to continued sunitinib plus IMA901 for a total of 10 vaccinations over a period of 4 months. The primary endpoint will be overall survival but we will also analyze a variety of other parameters including progression-free survival, safety, and survival in a predefined biomarker-positive subgroup. This is a pivotal phase 3 study currently being conducted in more than 100 centers in the US and Europe and we expect to have all 330 patients randomized early 2013; for information about specific sites please refer to www.clinictrials.gov

Dr. Figlin: When the trial is completed what would you hope to see in terms of improvement over current standard therapies?

Dr Reinhardt: We anticipate to see first clinical data mid 2014 with a final data set including the final overall survival analysis in early 2015. Based on the mechanism of action and the encouraging data from our phase 2 trial one would expect to see an increasing clinical effect of IMA901 over time and we clearly hope that this will translate into a relevant survival benefit of patients treated. While we have observed only modest activity of IMA901 on delaying early progression in our previous trials, one could hope that the simultaneous treatment with sunitinib may provide sufficient time to also see a prolongation of progression-free survival in patients treated with the combination of sunitinib and IMA901. At the same time we do expect a very benign safety profile based on the data from our previous phase 1 and 2 trials. KCJ

Antiangiogenic Therapies in RCC Elderly Patients

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Abstract

Background

Antiangiogenic (AA) therapies (sunitinib, sorafenib, bevacizumab) have demonstrated clinical activity in metastatic RCC. However, side effects are common, and might become an issue in elderly patients (pts), where toxicities such as fatigue, anorexia, and stomatitis might be more difficult to handle and could impair the quality of life, nutritional status and performance status. Thus, risk benefit in elderly patients might be questionable when using treatments that only prolong survival, but might alter quality of life. The goal of this study was to analyze toxicity and efficacy of angiogenesis inhibitor in metastatic RCC patients older than 75.

Methods

Between November 2004 and 2010, medical records of elderly patients (≥ 75 years) treated with AA therapies for advanced RCC in 7 French institutions were reviewed to assess safety and efficacy of targeted agents in such patients.

Results

73 patients were eligible, median age 77 (range: 75-86). Comorbidities: hypertension (36 pts, 49%), coronary artery disease or chronic heart failure (12 pts, 16 %) , arrhythmia (14 pts, 18%). Median ECOG performance status was 1 (range: 0-2), 55 patients (72 %) patients have lung metastases and 18 patients (25 %) liver metastases. Patients were treated with sunitinib (30 pts), sorafenib (41pts), and bevacizumab (2 pts in front line metastatic). The median overall survival was 18.6 months for all patients. Best response was partial response in 26 patients (35 %) and stable disease in 30 patients (41%). The median progression-free survival (PFS) in first- line treated was 10 months with sunitinib and 8,6 months with sorafenib. The median PFS of patients treated in second line with sorafenib was 10.3 months. Grade 3-4 toxicities were observed in 37 patients (50 %), including hematologic (8 pts, 11%), skin toxicity either hand foot syndrome (4 pts) or cutaneous rash (3 pts), mucositis (2 pts), hypertension (6 pts), fatigue (13 pts), and diarrhea (4 pts). There was no toxic death reported in relation with antiangiogenic therapies.

Conclusions

This retrospective study shows that treatment with AA is feasible with good efficacy in elderly patients. Efficacy observed especially with sorafenib, supports the use of AA in this subsetelederly pts. Antiangiogenic therapies warrant prospective study in older patients and the clinical benefits must be carefully weighed with the associated risks.

Introduction

Inhibition of angiogenesis has emerged as an important therapeutic strategy in a variety of solid tumors.[1] This is particularly true in patients with metastatic renal cell carcinoma (RCC), who could potentially benefit from three approved angiogenesis inhibitors that target vascular endothelial growth factor (VEGF) signaling (bevacizumab, sunitinib, sorafenib).[2,3,4,5] There are now five approved targeted agents, i.e. sorafenib, sunitinib, temsirolimus,[6] bevacizumab (in combination with interferon) and everolimus,[7] that have been shown to improve the outcome in patients with metastatic clear cell renal cell carcinoma (mRCC), in randomized controlled trials (RCTs). Recently, several other antiangiogenics with a different spectrum of activity and a different safety profile are currently under evaluation, including axitinib and pazopanib.

The incidence (*Editor's note: Axitinib was recently approved by the FDA*) of cancer in the elderly is increasing dramatically in European countries and in North America. More than 30% of patients diagnosed with cancer each year are aged >75 yr.[8] This demographic trend has led to the development of geriatric oncology.[9] Approximately half of all patients with new RCC diagnoses are made in patients 65 years of age or older.[10]

Keywords: elderly patients, RCC, targeted therapy, antiangiogenic

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Table 1. Patient Characteristics

Characteristics	N=73 pts (% of patients)
Gender Male vs Female	53 vs 20
Median age in years (range)	77,7 (75-88)
ECOG 0- 1 vs ≥ 2	(24 -35) vs 11
Number of comorbidities : median, (range)	2 (0-6)
Cardiovascular risk factor	55 (75 %)
Hypertension	36 (51 %)
Tabacco Intoxication	5 (7 %)
Dyslipidemia	14 (19%)
Diabetes	6 (8 %)
Cardiovascular diseases (history of myocardial infarction, congestive heart failure, arteritis,)	12 (16 %)
Cerebrovascular stroke history	5 (7 %)
Arrhythmia or pace maker	14 (19 %)
Sensitive disturbance (surdity, peripheral neuropathy, ophthalmic disease)	13 (18 %)
Chronic renal deficiency (GFR ≤ 60 ml/min)	24 (33 %)
Deep vein thrombosis or pulmonary embolism history	2 (3 %)
Arthrosis or bone pain	11 (15%)
Other cancer (prostate, breast, hepatocarcinoma, thryoid)	7 (9 %)
Histology tumor : RCC vs other	69 / 4
Metastatic site	
Number median (range)	3 (1-6)
Lung / Liver	55 (72 %) / 18 (25 %)
Lymph nodes / mediastinal / retroperitoneal	27 (37 %) / 18 (24 %)/ 17 (23%)
Bone	25 (34%)
Brain	3 (4 %)
Adrenal gland	13 (18 %)
Pancreas	5 (7 %)
Cutaneous or Thyroid	5 (7 %)
MSKCC Classification	
Good / Intermediate	18 / 39
Poor	3
Unknown	13

3 Missing data
**Risk factors associated with shorter survival according to the Memorial Sloan-KetteringCancer Center (MSKCC) risk classification: are a low serum hemoglobin level, an elevated corrected serum calcium level, an elevated serum lactate dehydrogenase level, a poor performance status, and an interval of less than 1 year between diagnosis and treatment (Motzer et al, 2002).

Table 2. Treatment Characteristics

Patient treatment	N (% of patients)
Previous therapy	
0 lines	47 (64 %)
1 line	18 (25 %)
>1 lines	8 (11 %)
Previous cytokines based regimens	23 (32 %)
IFN	15 (21 %)
IL-2 or IL-2/IFN	8 (11 %)
Others	
MPA	3 (4 %)
Chemotherapy	3 (4 %)
Experimental drugs	3 (4 %)
Anti-VEGF therapies	4 (5 %)
Treatment after 75 years	
Sunitinib	30 (41 %)
Sorafenib	41 (56 %)
Bevacizumab	2 (3 %)
Number of pts treated after	33 (45 %)
Best Response (PR,/ SD,/ PD)	
Sunitinib	12 / 11 /5
Sorafenib	14 / 19 / 6
Grade 3 or 4 toxicities	
Global incidence	37 (50%)
ECOG 0 vs vs ≥ 1 †	11 / 26
MSKCC good vs intermediate or poor ††	9 / 24
Comorbidities 0-1 vs ≥ 2	12 / 25

**Gemcitabine (1), ET743 (1)
***Thalidmoide (1), Neovastat (2), MPA (3), chemotherapy (1)
****4 patients received sorafenib (1pts), sunitinib (1pts), bevacizumab (1 pts), sunitinib and bevacizumab (1 pts) before 75 years age
*****4 patients not evaluable
† 3 missing datas
†† 13 missing datas

Data from phase III trials (level 1 evidence) are an essential element in the clinical decision. However, there are inevitably questions that large randomized clinical trials have not directly addressed. This is the case for major subgroups of the mRCC population, e.g. the elderly and those with comorbidities. Presently, no data are available based on clinical trials or EMEA publications. Only one retrospective analysis based on Target Study was found about patient with age > 70 years (n=115). In balance the progression free survival and the toxicity, a clinical benefit seems to be equivalent with younger patients. Nevertheless, many medical oncologists are still reluctant to use antiangiogenic therapies in very elderly patients with CRPC because of concerns about tolerance. Past experiences with cytokines highlight the difficulty to fit IL2 or INF in elderly patient. For example, in PERCY study, the mean age was 55 years with an oldest patient with 74 years.[11] Due to the common toxicities observed with antiangiogenic therapies, the safety of molecular targeted therapies in elderly patients is a major question. Medical history of elderly patient, generally include some cardiovascular risks as high blood hypertension, coronaropathy, cardiovascular arrhythmia, diabetes or renal deficiency.[10,12] There are only few studies about safety and efficacy in elderly patients with sorafenib.[13] Moreover, controversy over the age separating elderly and non-elderly patients continue. Even if some guidelines define elderly as > 65 years of age, physiological age seems also to be a more relevant information.[14]

Table 3. Clinical and Hematologic Toxicity in Elderly Patients

Grade ¾ Adverse events	Sunitinib treated pts (n=30)	Sorafenib treated pts (n=41)	Phase III Sunitinib, (Motzer et al, 2007)	Phase III Sorafenib (Escudier et al, 2007)
All events	19 (63 %)	18 (43 %)	-	-
Fatigue	5 (16 %)	8 (19 %)	7 %	5 %
Hypertension	5 (16 %)	1 (2.4 %)	8 %	4 %
Hematologic	8 (26 %)	1 (2.4 %)	5 %	UK
Thrombocytopenia	7 (23 %)	1 (2.4 %)	8 %	UK
Diarrhea	-	4 (10 %)	5 %	2 %
Nausea / vomiting	-	-	7 %	1 %
Mucositis	1 (3 %)	1 (2.4 %)	1 %	UK
Weight loss and anorexia	1 (3 %)	2 (4.8 %)	-	< 1 %
Cutaneous	1 (3 %)	7 (17 %)	-	-
Hand-foot syndrom	1 (3 %)	3 (7 %)	5 %	6 %
Rash	1 (3 %)	2 (4.8 %)	1 %	1 %
Pulmonary embolism	1 (3 %)	0	UK	UK
Cerebrovascular ischemia	1 (3 %)	0	UK	UK
Proteinuria or acute renal failure	3 (10 %)	0	UK	UK

The aim of this study is to evaluate for the first time the safety and the efficacy of antigiogenic therapies in significantly older patients with advanced RCC (patients ≥75 years) based on a multicenter experience.

Patients and Methods

Patients

Using a computerized database and systematic chart reviews, we identified the records of all patients with advanced RCC with age ≥75 years old treated with antiangiogenic therapies (Sunitinib, Sorafenib, Bevacizumab) in seven French institutions: Institut Gustave Roussy (B Escudier), Centre Léon Bérard (S Negrier), Centre Hospitalo Universitaire de Bordeaux (A Ravaud), Institut Jean-Godinot (JC Eymard), Centre Hospitalo Universitaire Bichat Beaujon (JM Rodier), Centre Paoli Calmette, Marseille (G Gravis), Groupe Hospitalier Universitaire de la Pitié Salpétrière (O Rixe).

For all patients, the following data were collected from the patients' medical history: age, comorbidity (arterial hypertension, cardiovascular disease, coronary artery disease, CHF, arrhythmia, diabetes), number of prescribes drugs, histology (Clear cell versus non Clear cell), site and number of metastases, MSKCC risk category,[15] Eastern Cooperative Oncology Group Performance Status (ECOG, PS), previous treatments, antiangiogenic therapies (sorafenib sunitinib, Bevacizumab), toxicities grade 3/4 according to the National Cancer Institute common Toxicity Criteria 3.0, dose reduction, best response to treatment and efficacy, PFS and OS.

Statistical Analysis

Qualitative data were compared by the Chi 2 test or the Fisher exact test as appropriate. Association between MSKCC, comorbidities and toxicities was determined by univariate analysis using the Chi2 test or Fisher Exact test. The progression free survival and overall survival were computated by Kaplan-Meier method. All comparison tests were to sided and p value < 0.05 were considered statistically significant. Statistical analysis was done with R version 2.7.1 .

Results

Patient Characteristics

A total of 73 patients (pts), median age of 77 years old (range: 75-88), with advanced RCC treated at seven different institutions in France between June 2005 and June 2010, and who had received antiangiogenic thera-pies were included in this analysis. Main characteristics of patients are summarized in **Table 1**.

Most patients have comorbidities (median 2; range 0-6): arterial hypertension (52 %), or other cardiovascular risk factor (75%) such as coronary artery disease/ Congestive Hear Failure (16 %), arrhythmia (19%) and dyslipidemia (19 %). No comorbidity was reported in 7 patients (10%) and less than one in 14 patients (19%).

Median ECOG performance status was 1 (range: 0-2), and a large part of patient (85 %) has a good performance status (ECOG < 2). Nevertheless, most of them could be considered at frailty risk, encompassed comorbidity as arthrosis or bone pain (15 %), renal deficiency (32 %), anorexia (7 %) and mood depressed (11%). The geriatric syndrome including sensorial or motricity deficiency, hypoacousia, ocular deficiency, neurologic diseases (Parkinson, cerebrovascular sequelae) is reported in 17 patients (23%). Other cancer disease history (prostate, breast, thyroid, hepatocarcinoma) were present in 7 patients (10 %).

The prognostic factors groups for renal cell carcinoma were as follow: 14 pts had low-risk disease , 28 had intermediate risk disease, and 2 pts were in the poor risk group (13 pts with missing data). Moreover, 72% of patients had lung metastases, 25% liver metastases. Bone metastasis were reported in 25 patients (34 %) and never as a single localization.

Treatments and Antiangiogenic Therapies

First line of antiangiogenic treatment was administrated in 47 pts (64%) and most of the patient had received previous immunotherapy (23 pts, 31%) or angiogenesis inhibitor (4 pts, 5%).

Patients were treated by sunitinib (22 pts in first line, 7 pts in second line and one pt in third line) with a median time of 7.7 months, sorafenib (22 pts in first line, 15 pts in second line and 4 pts in third or more line) with a median time of 7.3 months. Moreover, two patients were treated with bevacizumab (2 pts in first line). Sixty four (87%) patients were started at full dose, 4 pts at 75% dose, and 5 (10%) patients at half dose (**Table 2**).

Safety

Many patients experienced grade 3-4 toxicities (37 pts; 50%), including cutaneous toxicity as hand foot syndrome (4 pts) or cutaneous rash (3 pts) and mucositis (2 pts), hypertension (6 pts), fatigue (13 pts), diarrhea (4 pts), proteinuria and acute renal failure (4 pts). In the sorafenib group, dose interruption related to grade 3-4 toxicity occurred in 22 pts and 2 pts rechallenged with 50% of reduction dose due to diarrhea. Discontinuation related to grade 3 or 4 toxicities occurred in 2 pts treated with sunitinib. One patient experienced congestive heart failure under sunitinib treatment. In the bevacizumab group (2 pts) no grade 3 or 4 toxicities were notified. No Diabetes disturb or metabolic complication were reported during sunitinib or sorafenib treatment. Multiples grade 3-4 toxicities occurred in 21 patients and more than 2 events in 5 pts (7%). There was no toxic death reported in relation with antiangiogenic therapies (**Table 3**).

The great majority of patients had good performances status (82%), only 11 patients (15%) have an ECOG ≥ 2. The incidence of grade 3/4 toxicities was not different for patients with ECOG 0 and ECOG≥ 1 (p=0.74) and different group of patients according to the MSKCC risk score (good and intermediate or poor, p=0.82). Finally, comorbidities were frequent, 48 pts (65 %) have at least 2. Number of comorbidity or all comorbidities with an incidence ≥ 5 % (**Table 1**) were not associated the incidence of grade 3-4 toxicities or multiples grade 3-4 toxicities (p> 0.10).

Efficacy

The median overall survival was 18,6 months IC_{95} [17.7;28,7] for all patients (**Figure 1**). According to the MSKCC criteria overall survival (**Figure 2**) was different in good and intermediate group of patient with respectively a median of 31.8 and 18.3 months (p=0.02, 13 patients not evaluable). Best response was partial response in 26 pts (36 %) and stable disease in 30 pts (41 %). The median PFS in first line treatment was 10 months IC_{95} [5.8;Not Reached (NR)] with sunitinib (**Figure 3A**) and 8,6 months IC_{95} [5.4; 27.7] with sorafenib (**Figure 3B**). The median PFS of patients treated in second line with sorafenib was 10.3 months IC_{95} [4.3; 13.7] (**Figure 3C**) .

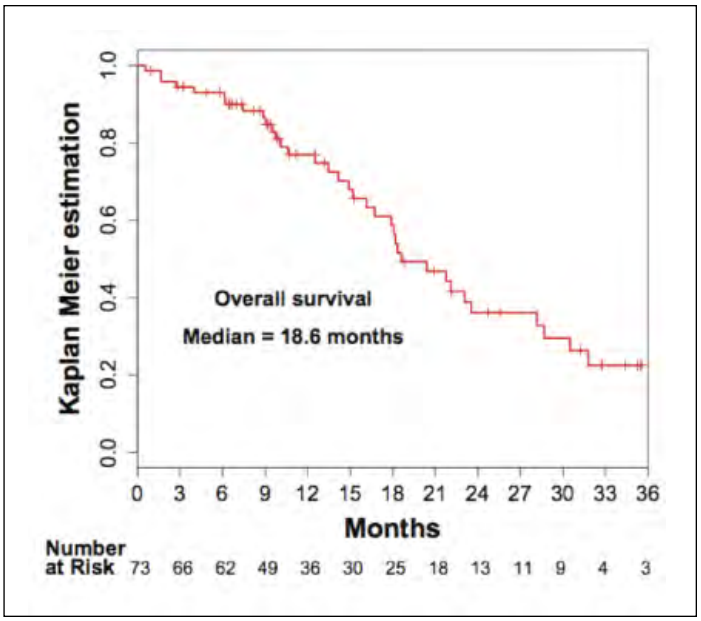

Figure 1. Kaplan-Meier estimation for overall survival

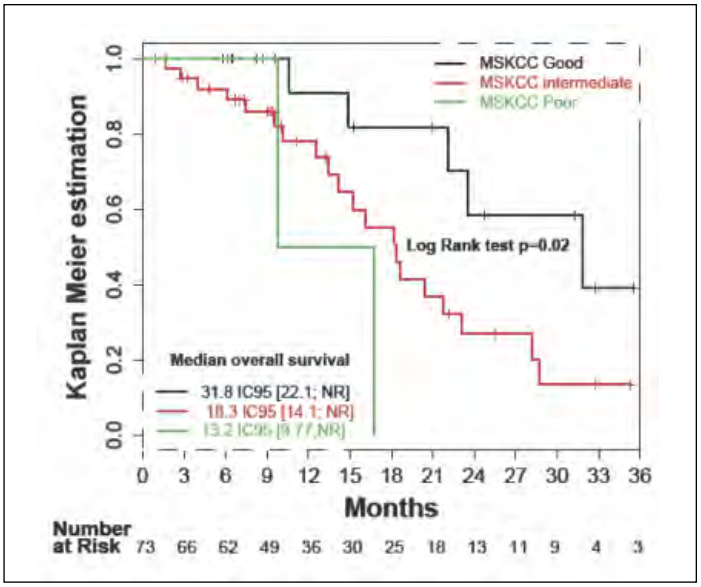

Figure 2. Kaplan Meier estimation for overall survival against MSKCC prognostic factor

Discussion

To the best of our knowledge, this is the first study assessing the use of antiangiogenic therapies in daily routine practice among very elderly patients with advanced RCC in different institutions. This is the largest retrospective analysis of antiangiogenic treatment in elderly patients with advanced RCC. The lack of such studies is probably due to the fear of physicians to treat elderly patients with antiangiogenic therapies. Only few patients were elderly in large randomized clinical trials, reflacting the well-recognized underrepresentation of patients older than 70 in clinical trials.[16] In advanced cancer care, elderly patients are at risk of receiving sub-optimal therapy and the exclusion from clinical trails enhanced this situation. In part, this may

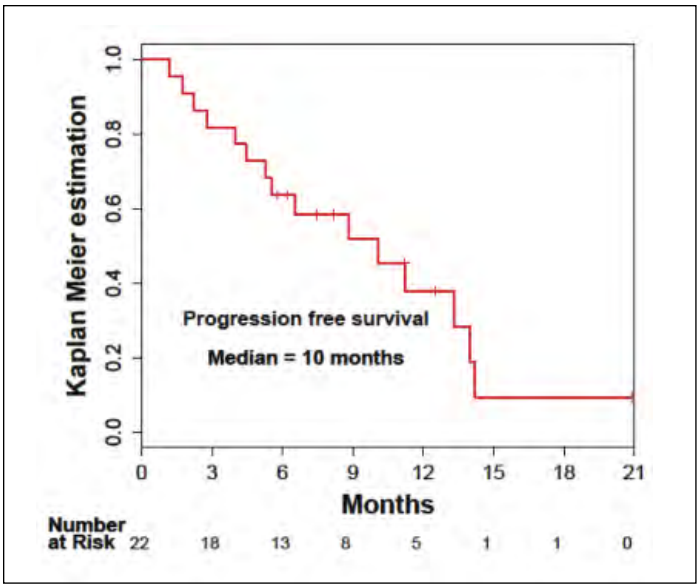

Figure 3A. Kaplan-Meier estimation for progression free survival in (A) sunitinib first line treatment group.

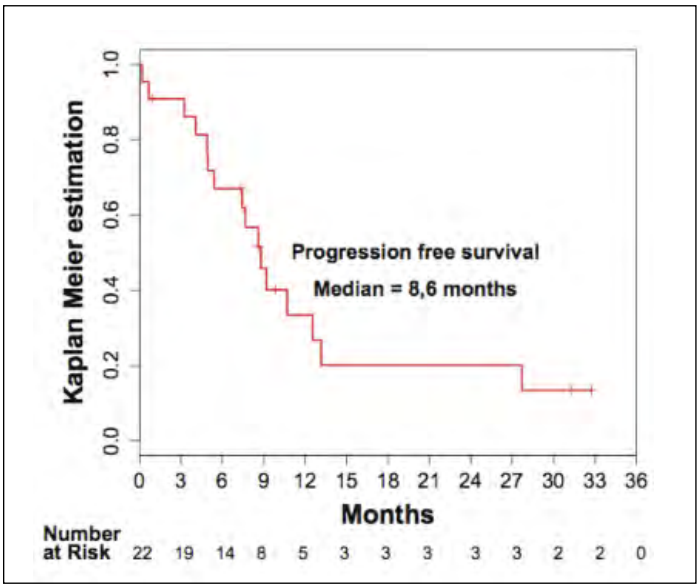

Figure 3B. Sorafenib first line treatment group.

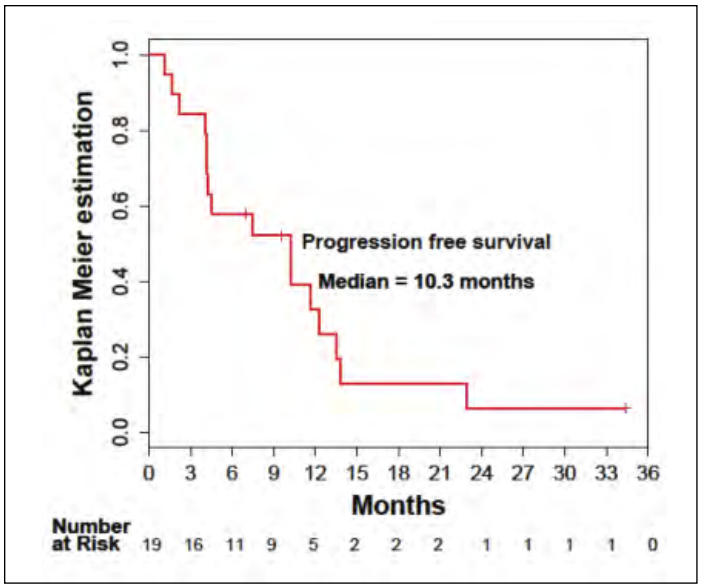

Figure 3C. Sorafenib second line treatment group.

reflect patients'preference to avoid aggressive interventions, but it may also reflect the bias of clinicians, or the lack of relevant clinical data and management guidelines.

In the present study, we have shown that serious adverse events related to VEGF inhibitors are common (50 %) in patient ≥ 75 years with advanced RCC, but usually manageable. Lack of death related toxicity and good overall survival are in favor of antiangiogenic therapies in these elderly pts. PS, MSKCC risk score, presence of comorbidities were associated with the occurrence of acute severe toxicity. Elderly patients are generally more vulnerable to hematologic toxicity, which is the most common and the most frequent fatal complication of chemotherapy. They are also probably more vulnerable to gastro intestinal toxicities or cardiovascular side effects, which are frequent with antiangiogenic therapies.[17]

Our study suggest that antiangiogenic therapies in elderly patients with RCC is feasible, with no toxic death, and with similar antitumor activity compared to phase III trials results. Recently, a retrospective analysis of data from the phase III randomized TARGET (Treatment Approach in Renal cancer Global Evaluation Trial) examined the safety and efficacy of sorafenib in patients with age > or =70 years and < 70 years.[13] This trial did not evaluate the subpopulation of very elderly patients (age ≥ 75 years), but,it appears that patients aged over 65 years benefit as much from targeted therapies as younger patients and do not experience more frequent or severe toxicity. In this study, older patient (ie, 70 years or older) constituted 12.7% of the TARGET study population. This study shows that outcomes in older patients and younger patients ate the same with no difference in PFS. Adverse events were manageable regardless of age. The most frequent adverse events in older patients treated by sorafenib were rash, diarrhea, fatigue, anorexia and hand-foot syndrome. Cardiac toxicities (cardiac ischemia, left ventricular dysfunction) were reported in 10 (2.6%) younger patients versus three (4.3%) older patients treated by sorafenib. Few large studies evaluate safety and efficacy of antiangiogenic in mRCC in very elderly patients. Treatments currently recommended for metastatic renal cell cancer (mRCC) have not been evaluated specifically in elderly patients. Different subgroup analysis of large CRTs according to age evaluated the efficacy and toxicity data from phase III trials or expanded access program of the targeted agents sorafenib (Nexavar®), sunitinib (Sutent®), temsirolimus (Torisel®), and bevacizumab (Avastin®).[10]

Moreover pooled analysis of bevacizumab trials in colon cancer indicates that adding bevacizumab to fluorouracil-based chemotherapy improved OS and PFS, similar to the benefits in younger patients (>/= 65 years),

without more toxicities in elderly patients.[18,19]

However, several studies suggest that benefit of antiangiogenic therapies could be restricted to younger patients. Recently, bevacizumab demonstrated clinical benefit in addition to standard chemotherapy in advanced non-small cell lung carcinoma (NSLC) (AVAIL,AV).[20,21] Nevertheless, in elderly NSCLC patients, paclitaxel carboplatin bevacizumab combination was associated with a higher degree of toxicity, but no obvious improvement in survival compared with the paclitaxel-carboplatin regimen.[22]

We did not observe any toxic death in our retrospective study. In contrast, 50% of pts experienced of grade 3-4 toxicities and their incidence seems to be twice to the rate of toxicities reported with sunitinib and sorafenib in phase III trials.[3,4] Several molecular targeted therapies have clearly improved overall survival and the quality of life of patients with advanced RCC. Nevertheless, these drugs have some target related adverse effects, particularly cardiovascular toxicities.[23] The management of cardiovascular toxicity or GI toxicities is a major issue in daily practice, in particular in elderly patients or patients with cardiovascular comorbidities. Up to two thirds of 75 year old pts with kidney cancer have cardiovascular comorbidities such as hypertension, cardiovascular disease or diabetes.[12] In our studies, severe toxicities had been registered but were reversible. Most of patients have a good performance status or MSKCC risk score, which can suggest that clinician have made in balance the benefit risk ratio in their patients. The lack of treatment opportunity before the area of anti-angiogenic treatment could be engaged the oncologist to propose this treatment. Moreover, the median time overall survival since metastatic status Based on these results, antiangiogenic therapies should be discussed in elderly patients with advanced RCC following the recent recommendation of SIOG.[10]

Despite the usual limitations of a retrospective study, our results indicate that patients ≥ 75 yr of age considered fit for the cancer treatment had a similar safety and efficacy profile to younger patients. In our study, response rate and PFS are very close to those seen in patients enrolled in clinical trial. Nevertheless, comprehensive geriatric assessment can predict tolerance to cancer treatment, morbidity, and mortality in older cancer patients more accurately than PS or a simple numeric evaluation of comorbidities.[24,25] For example, the International Society of Geriatric Oncology has recently proposed guidelines for the management of older prostate cancer patients based on several geriatric scales.[17] Moreover, our results must be confirmed in a prospective evaluation of antiangiogenic therapies in elderly patients.

Conclusions

In summary, we have shown that selected elderly patients have the potential to derive benefit from sequential antiangiogenic therapies with significant increase in manageable grade 3 toxicity. Nevertheless, this retrospective study shows that treatment with AA is feasible and effective in elderly pts. Therefore, antiangiogenic therapies should not be withheld from these patients purely on the basis of chronologic age.

A multidisciplinary team including oncologist, cardiologist, dermatologist, nephrologist, pharmacists and geriatricians, is necessary to optimize daily practice and evaluation of angiogenesis inhibitors in elderly patient. Indeed, geriatric tools should be used to more accurately detect elderly RCC patients who are unfit for AA or at risk of severe toxicity. Moreover, acute toxicities should be prevent or anticipated to prevent severe organs dysfunction in patient with comorbidities. Age by itself should not be used as a criterion to deny patients with RCC potentially effective targeted therapies. Antiangiogenic therapies warrant prospective and multicenter specific trials dedicated to elderly patients to address specific problem and management which may be offered to a broader group of elderly patients.

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detailed findings from TIVO-1 for presentation at the 2012 Annual Meeting of the American Society of Clinical Oncology (ASCO) being held June 1-5, 2012 in Chicago.

FDA Approves INLYTA® (axitinib) for Patients With Previously Treated Advanced RCC

NEW YORK—The spectrum of therapy in kidney cancer has expanded to 7 drugs with the FDA approval of INLYTA® (axitinib), a tyrosine kinase inhibitor, for the treatment of patients with advanced renal cell carcinoma (RCC) after failure of one prior systemic therapy. The approval is based on data from the Phase 3 AXIS trial, which demonstrated that axitinib significantly extended progression free survival (PFS) [HR=0.67, 0.54-0.81, *P*<0.0001] with a median PFS of 6.7 months (95% CI: 6.3, 8.6) compared with 4.7 months (95% CI: 4.6, 5.6) for those treated with sorafenib, a current standard of care for this patient population, representing a 43% improvement in median PFS compared to sorafenib. Axitinib is the first treatment to demonstrate superior benefit in a Phase 3 study compared with another targeted agent in advanced RCC

Cancers of the kidney and renal pelvis are among the 10 most commonly diagnosed cancers in the United States. Approximately 13,000 individuals die of advanced RCC in the U.S. each year. Approximately 60,000 new cases of this tumor are diagnosed in the U.S. annually[1], about 20 percent of which have advanced disease at the time of diagnosis.[1] Between 40 and 65 percent of patients who progress following first-line therapy go on to receive a second-line treatment.

Axitinib, introduced by Pfizer, is an oral therapy that was designed to selectively inhibit vascular endothelial growth factor (VEGF) receptors 1, 2 and 3, receptors that can influence tumor growth, vascular angiogenesis and disease
progression.

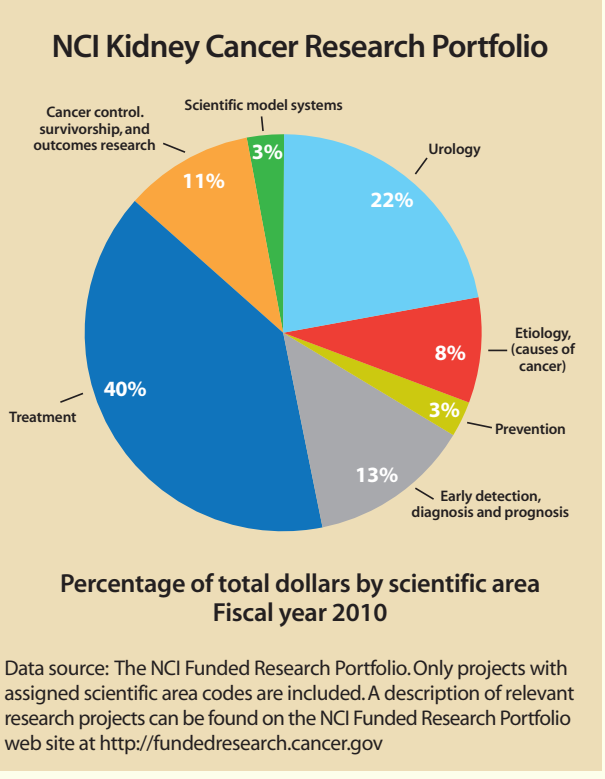
"Through studying this drug we have learned that a VEGFR-targeted therapy can be effective following prior treatment options, including another VEGFR-targeted agent. This is important in helping physicians understand where these medications fit in the treatment armamentarium," said Brian I. Rini, Taussig Cancer Institute at Cleveland Clinic, who served as principal investigator of the study.

"The FDA approval of this new treatment represents a significant benefit for the many patients who are living with this type of kidney cancer and who are in need of additional treatment options," said William Bro, chief executive officer of the Kidney Cancer Association.

Axitinib is also being investigated in a randomized clinical trial in patients with treatment-naïve as well as previously treated advanced RCC, and in a randomized Phase 2 clinical trial for the treatment of hepatocellular carcinoma (HCC). Additionally, under a collaborative development agreement between Pfizer and SFJ Pharma Ltd. II, SFJ will conduct a Phase 3 clinical trial in Asia studying axitinib for adjuvant treatment of patients at high risk of recurrent RCC following nephrectomy.

Funding for Kidney Cancer Research: Where Does NCI Money Go?

BETHESDA, MD—How does the National Cancer Institute allocate its funding for kidney cancer research? A chart of the percentage of total dollars by scientific area provides a good snapshot of where the money is going. KCJ



Data source: The NCI Funded Research Portfolio. Only projects with assigned scientific area codes are included. A description of relevant research projects can be found on the NCI Funded Research Portfolio web site at http://fundedresearch.cancer.gov

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apy should be continued after CR. A multicenter, retrospective analysis of a series of patients with mRCC who obtained CR during treatment with TKIs (sunitinib or sorafenib), either alone or with local treatment (surgery, radiotherapy, or radiofrequency ablation), was performed. CR was identified in 64 patients; 36 patients had received TKI treatment alone and 28 had also received local treatment. Most patients had clear cell histology (60 of 64 patients), and all had undergone previous nephrectomy. The majority of patients were favorable or intermediate risk; however, three patients were poor risk. Most patients developed CR during sunitinib treatment (59 of 64 patients). Among the 36 patients who achieved CR with TKI alone, eight continued TKI treatment after CR, whereas 28 stopped treatment. Seventeen patients who stopped treatment (61%) are still in CR, with a median follow-up of 255 days. Among the 28 patients in CR after TKI plus local treatment, 25 patients stopped treatment, and 12 of these patients (48%) are still in CR, with a median follow-up of 322 days.
Conclusion: CR can occur after TKI treatment alone or when combined with local treatment. CR was observed at every metastatic site and in every prognostic group.

Everolimus in metastatic renal cell carcinoma: Subgroup analysis of patients with 1 or 2 previous vascular endothelial growth factor receptor-tyrosine kinase inhibitor therapies enrolled in the phase III RECORD-1 study.

Calvo E, Escudier B, Motzer RJ, et al. *Eur J Cancer*. 2011;Dec 30. [Epub ahead of print]
Summary: In the phase III RECORD-1 trial (ClinicalTrials.gov: NCT00410124), patients with metastatic renal cell carcinoma (mRCC) who progressed on previous vascular endothelial growth factor receptor-tyrosine kinase inhibitor (VEGFr-TKI) therapy were randomized 2:1 to everolimus 10mg once daily (n=277) or placebo (n=139). Median progression-free survival (PFS) was 4.9 months with everolimus and 1.9 months with placebo (hazard ratio [HR], 0.33; P<.001). This preplanned, prospective sub-analysis evaluated PFS benefit of everolimus vs placebo in patients who had previously received 1 or 2 VEGFr-TKIs. Median PFS was estimated using the Kaplan-Meier method, and Cox proportional hazards model was used to analyze differences in PFS. All patients (100%) received 1 previous VEGFr-TKI; 26% of patients received 2 previous VEGFr-TKIs. Among patients who received 1 previous VEGFr-TKI, median PFS was 5.4months with everolimus and 1.9months with placebo (HR, 0.32; 95%confidence interval [CI], 0.24-0.43; P<.001). Among patients who received 2 previous VEGFr-TKIs, median PFS was 4.0months with everolimus and 1.8months with placebo (HR, 0.32; 95%CI, 0.19-0.54; P<.001). The everolimus safety profile was similar for both groups.
Conclusion: Everolimus was associated with prolonged PFS relative to placebo in patients who received 1 or 2 previous VEGFr-TKIs. Patients who received only 1 previous VEGFr-TKI had apparently longer PFS with everolimus in reference to those who received 2 previous VEGFr-TKIs. These results support the use of everolimus as the standard of care in patients who fail initial VEGFr-TKI therapy.

Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial.

Rini BI, Escudier B, Tomczak P, et al. *Lancet*. 2011;378: 1931-1939
Summary: The treatment of advanced renal cell carcinoma has been revolutionized by targeted therapy with drugs that block angiogenesis. So far, no phase 3 randomised trials comparing the effectiveness of one targeted agent against another have been reported. We did a randomised phase 3 study comparing axitinib, a potent and selective second-generation inhibitor of vascular endothelial growth factor (VEGF) receptors, with sorafenib, an approved VEGF receptor inhibitor, as second-line therapy in patients with metastatic renal cell cancer. We included patients coming from 175 sites (hospitals and outpatient clinics) in 22 countries aged 18 years or older with confirmed renal clear-cell carcinoma who progressed despite first-line therapy containing sunitinib, bevacizumab plus interferon-alfa, temsirolimus, or cytokines. Patients were stratified according to Eastern Cooperative Oncology Group performance status and type of previous treatment and then randomly assigned (1:1) to either axitinib (5 mg twice daily) or sorafenib (400 mg twice daily). Axitinib dose increases to 7 mg and then to 10 mg, twice daily, were allowed for those patients without hypertension or adverse reactions above grade 2. Participants were not masked to study treatment.
The primary endpoint was progression-free survival (PFS) and was assessed by a masked, independent radiology review and analyzed by intention to treat. This trial was registered on ClinicalTrials.gov, number NCT00678392. A total of 723 patients were enrolled and randomly assigned to receive axitinib (n=361) or sorafenib (n=362). The median PFS was 6·7 months with axitinib compared to 4·7 months with sorafenib (hazard ratio 0·665; 95% CI 0·544-0·812; one-sided p<0·0001). Treatment was discontinued because of toxic effects in 14 (4%) of 359 patients treated with axitinib and 29 (8%) of 355 patients treated with sorafenib. The most common adverse events were diarrhea, hypertension, and fatigue in the axitinib arm, and diarrhea, palmar-plantar erythrodysaesthesia, and alopecia in the sorafenib arm.
Conclusion: Axitinib resulted in significantly longer PFS compared with sorafenib. Axitinib is a treatment option for second-line therapy of advanced renal cell carcinoma. KCJ

EDITOR'S MEMO

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But there are more exciting trends on the horizon. We have seen how Phase 3 clinical trials are looking at the use of new multipeptide vaccines that could make an important contribution toward expanding the spectrum of care. This is an exciting development, particularly in view of their use with a tyrosine kinase inhibitor that could improve the immune response. This is hardly a sci-fi vision of the future. It is happening now and it is an important development in our effort to manage this disease.

From thousands of identified tumor-associated peptides (TUMAPs) the most suitable ones are selected and combined to a single multi-peptide product to form a therapeutic cancer vaccine. The goal is to provoke a number of specific T-cell responses which finally result in the destruction of tumor cells presenting the applied TUMAPs. Currently, there are two phase 3 trials evaluating the use of vaccines in renal cell carcinoma. It may not be a "nanoparticle shuttle" as envisioned by some researchers, but it's a big step that could usher in a bold new era in treatment of kidney cancer.

Robert A. Figlin, MD
Editor-in-Chief

1.*Accelerating Progress Against Cancer: ASCO's Blueprint for Transforming Clinical and Translational Cancer Research.* http://www.asco.org/ASCOv2/Department%20Content/Cancer%20Policy%20and%20Clinical%20Affairs/Downloads/Blueprint.pdf

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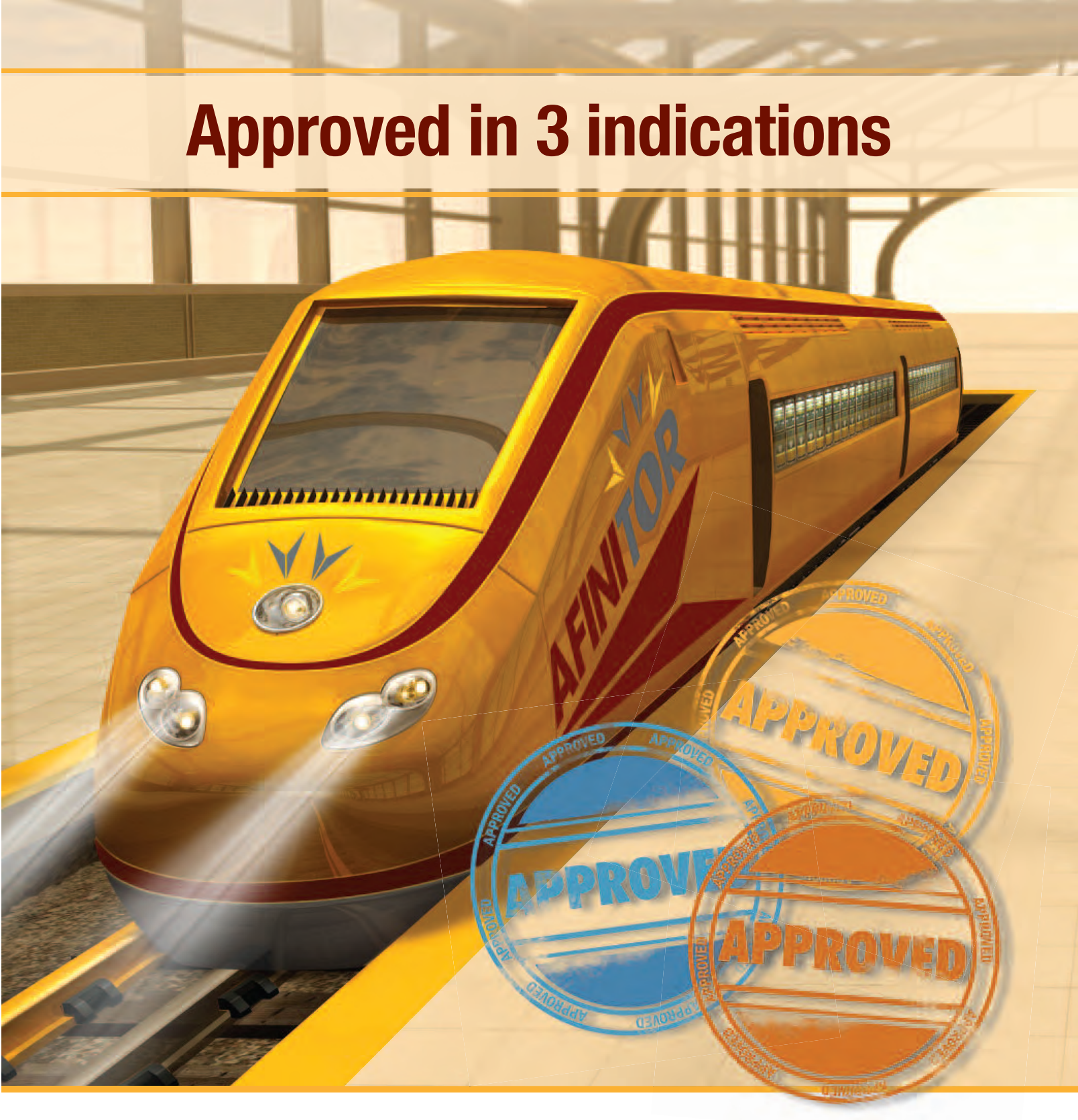

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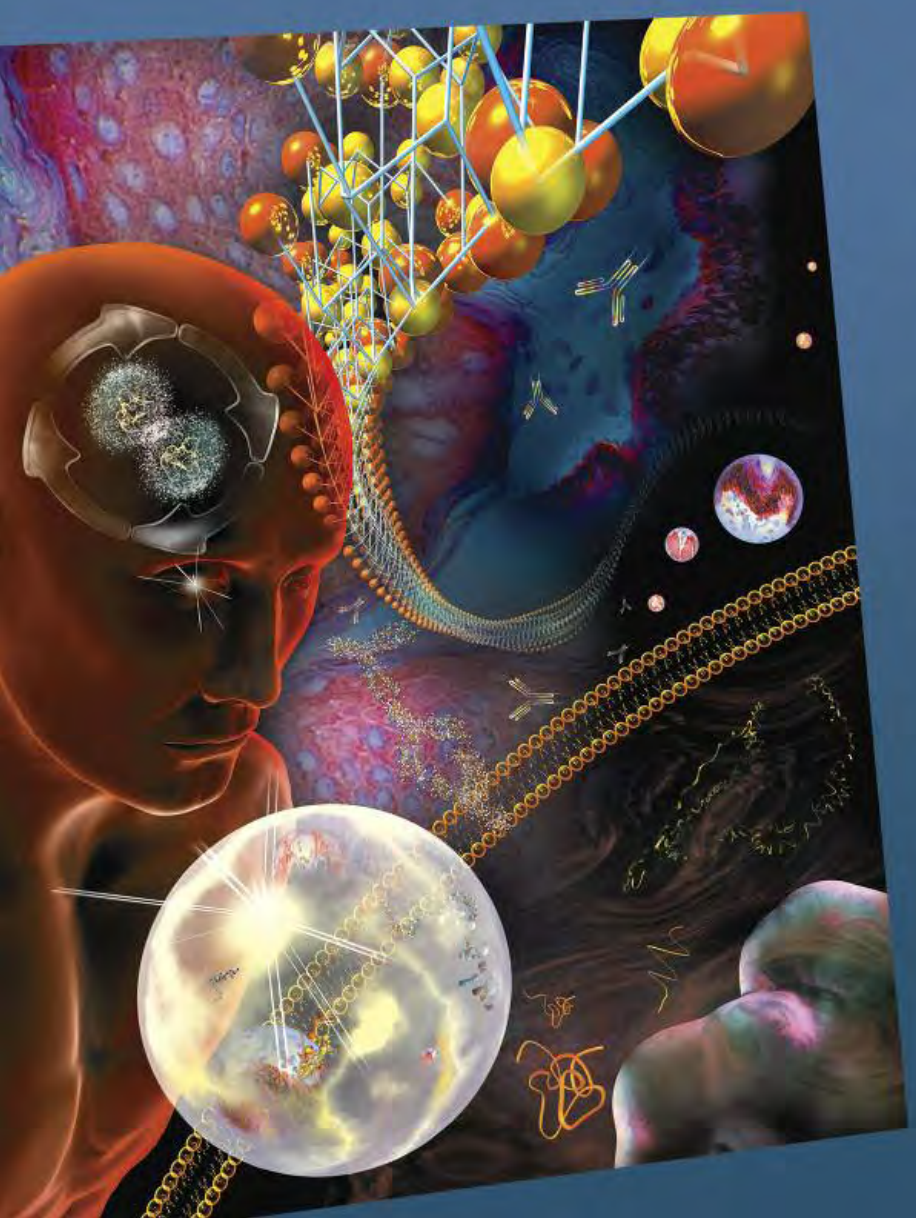

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