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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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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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Research Triangle Park, NC 27709

Kidney Cancer Journal Author Guidelines

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- 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.

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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
New findings are strengthening the association between smoking and kidney cancer, as seen on a light micrograph. The image in the micrograph is of a section through a malignant renal neoplasm (round, center) in the renal vein (c-shaped). Copyright, Photo Researchers.

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KCJ GUEST EDITOR'S MEMO

Rediscovering How We Treat Kidney Cancer and Modify Risky Behavior

Bernard Escudier, MD

New data that emerges from ongoing clinical trials of targeted therapies hold our attention throughout the year, and in recent years these new agents have vastly expanded the treatment spectrum. Although such news tends to overshadow other studies—such as those presenting epidemiologic data—it is worthwhile to turn our attention from time to time to basic research that gives us insights and benchmarks for evaluating our treatment paradigms and strategies to modify risk.

Two articles in this issue illustrate how we can deepen our awareness of trends in demographics, treatment, compliance, and risk stratification by returning to some fundamental research in these areas. One of our reports gathered data from a large retrospective, observational, cohort study extracted from private-practice databases of longitudinal, patient-level medical and pharmacy claims collected from physicians and other health care providers across the United States. It can help remind us of how clinicians are practicing in the era of targeted therapy and serves as a benchmark to determine how certain strategies are being followed.

Such information from "real-world" clinical practice is a necessary complement to information from clinical trials in informing clinical use and policy decisions that involve the new agents. The current study characterized patient characteristics, treatment patterns, and schedule compliance with molecular-targeted agents in a large, nationally representative cohort of patients with mRCC (N = 1080).

As we might expect, the most common first-line treatments were sunitinib and temsirolimus, and the most common second-line treatments were sunitinib and everolimus. The most common treatment sequence was sunitinib or everolimus after a first-line TKI (sunitinib/sorafenib). These treatment patterns should be interpreted with the knowledge that the line of therapy reported in this study was based on analysis of claim activities, which might not completely reflect patients' actual drug-taking behavior. However, these treatment choices and sequences appear to reflect application of findings from clinical trials and are consistent with current treatment guidelines, according to the authors. The article is worthwhile reading as a means of comparing our own strategies within the context of a broader analysis and helps us chart the standard of care.

By now it is axiomatic that smoking is linked with renal cell carcinoma, but new information is emerging on aspects of this association that enables us to do an even better job of counseling our patients in our efforts at behavior modification. For example, there are new insights on how nicotine promotes angiogenesis. And the question remains whether smoking itself is associated with the development of tumors that invade and metastasize more readily. Further study is needed to definitively link cigarette smoking to more aggressive RCC tumor biology and phenotype. However, cigarette smokers are more likely to present with more

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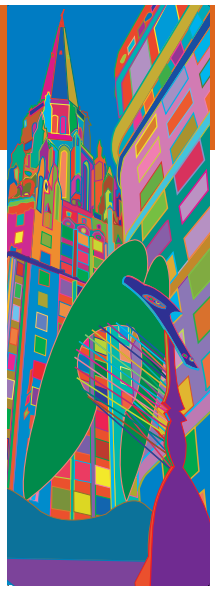

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Tracking Trends From Web-based Sources, Translational Research, the FDA, and Patient Registries

FDA Grants Fast Track to RENCAREX® for Adjuvant Therapy of Clear Cell Renal Cell Carcinoma

MUNICH—WILEX AG has announced that RENCAREX® has been granted Fast Track designation by the FDA. The drug is undergoing the pivotal phase 3 trial ARISER (Adjuvant RENCAREX Immunotherapy trial to Study Efficacy in non-metastasised Renal cell carcinoma) for the adjuvant treatment of patients with non–metastatic clear cell renal cell carcinoma (ccRCC) at high risk of relapse after surgery. WILEX has signed a licencing agreement for RENCAREX® with US partner Prometheus Laboratories.

"We are pleased with this decision from the FDA. No drug has been approved to date by the FDA or EMA [European Medicines Agency] for the adjuvant therapy of non–metastatic ccRCC. RENCAREX® was granted Orphan Drug status in the United States and in Europe and is of major relevance for those patients with this aggressive type of cancer," said Paul Bevan, PhD, Head of R&D and Member of the Executive Management at WILEX AG.

RENCAREX® is based on the antibody girentuximab, which binds to the tumor-specific antigen CA IX an antigen overexpressed in ccRCC. The therapeutic antibody makes the tumor visible to the endogenous immune system, recruiting natural killer cells that can destroy any existing cancer cells. RENCAREX® should inhibit the further growth and recurrence of ccRCC. ARISER is an international, multicenter, randomized phase 3 trial that examines the efficacy of the antibody RENCAREX® in comparison to placebo in the treatment of ccRCC patients following complete or partial surgical removal of the affected kidney in patients with no detectable metastases.

The ARISER trial involves 864 patients, who received the study medication in once-weekly infusions over a period of 24 weeks. The last patient completed treatment in February 2009. Following the occurrence of the 100th relapse, the first interim analysis for futility was carried out in late 2007. The Independent Data Monitoring Committee (IDMC) recommended that the trial be continued because it will probably deliver a significant result. The process of the interim analysis for efficacy has been started in the first quarter of 2011.

Early Blood Test Stratifies Renal Cell Carcinoma Patients for Progression-Free Survival on 2 Therapies

BROOMFIELD, CO—Data presented at the 10th International Kidney Cancer Symposium in Chicago showed that the pretreatment blood-based test, VeriStrat, was able to stratify patients with renal cell carcinoma (RCC) treated with a combination of 2 targeted therapies, sunitinib (Sutent®) and erlotinib (Tarceva®), by survival outcomes. Patients who tested VeriStrat Good had significantly longer progression free survival (PFS) and overall survival (OS) when treated with the combination therapy compared with patients who tested VeriStrat Poor.

The study retrospectively, and in a fully blinded fashion, applied the VeriStrat test to a subset of the patient population from a phase 1/2 clinical trial of erlotinib plus sunitinib in RCC patients. VeriStrat analysis was performed on all available serum samples. Thirty-seven of 46 patients were classified as either VeriStrat Good or VeriStrat Poor based on the VeriStrat algorithm developed for non–small cell lung cancer.

VeriStrat Good patients had a significantly longer PFS and OS versus VeriStrat Poor patients (PFS: median 12.3 vs 4.7 months, and OS: median 38.4 vs 11.6 months). There was a statistically significant correlation between VeriStrat classification and Heng prognostic criteria, but not MSKCC (Memorial Sloan Kettering Cancer Center) classification. VeriStrat showed the potential to further refine current grouping of RCC patients, separating MSKCC intermediate patients into VeriStrat Good and VeriStrat Poor subgroups with statistically significantly different PFS (log-rank $P = .030$).

Heinrich Roder, PhD, Chief Technology Officer of Biodesix said, "This data set shows that our test, VeriStrat, may be helpful in identifying specific and useful disease characteristics in RCC. It is also exciting to see that our test is showing utility across multiple solid tumors. Oncologists currently do not have a simple serum test that can be used across multiple tumor types. We are continuously engaging in additional studies to further explore the full clinical utility of VeriStrat."

Abstracts from the European Society of Medical Oncology and the European Multidisciplinary Cancer Congress, Stockholm , September 23-27, 2011

The European Multidisciplinary Cancer Congress reported an attendance of almost 16,000 from 116 countries, according to the European Society of Medical Oncology (ESMO). Notable abstracts in RCC included the following.

Abstract 7103

Escudier B, Loomis AK, Kaprin A, et al. Association of Single Nucleotide Polymorphisms in VEGF Pathway Genes With Progression-Free Survival and Blood Pressure in Metastatic Renal Cell Carcinoma in the Phase 3 Trial of Axitinib Versus Sorafenib (AXIS Trial)

In the randomized, open-label, phase 3 AXIS trial in second-line metastatic renal cell carcinoma (mRCC; clinicaltrials.gov NCT00678392), axitinib demonstrated a statistically significant improvement in progression-free survival (PFS) compared with sorafenib (median 6.7 vs 4.7 months; hazard ratio 0.665, $P < .0001$). This study also explored potential associations between germline single nucleotide polymor-

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Essential Peer-Reviewed Reading in Kidney Cancer

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

Patient Outcomes Improved With Targeted Therapy

Escudier B, Gore M. Axitinib for the management of metastatic renal cell carcinoma. *Drugs R D*. 2011; 11:113-126.

In the past few years, patient outcomes have significantly improved with the use of targeted agents for the treatment of advanced renal cell carcinoma (RCC). Several targeted agents are licensed for the treatment of metastatic RCC (mRCC), and a number of new agents are under investigation. Axitinib, a small molecule indazole derivative is an oral, potent multitargeted tyrosine kinase receptor inhibitor that selectively inhibits vascular endothelial growth factor receptors (VEGFR)-1, -2, and -3 at subnanomolar concentrations, in vitro. In various nonclinical models, axitinib has demonstrated in vivo target modulation and antiangiogenesis.

Pharmacokinetic studies have shown that 5 mg twice daily continuous daily dosing of axitinib administered orally with food, is rapidly absorbed and reaches peak concentrations within 2 to 6 hours.

Axitinib is metabolized primarily in the liver via the cytochrome P450 (CYP) system and less than 1% of the drug passes unchanged in the urine. The pharmacokinetics of axitinib do not appear to be altered by coadministered chemotherapies, and antacids do not have a clinically significant effect. Coadministration with CYP3A4 and 1A2 inducers is contraindicated. In addition, proton pump inhibitors reduce the rate of axitinib absorption.

Increased axitinib exposure is associated with higher efficacy indicated by decreased tumor perfusion and volume. In phase 2 clinical trials in patients with advanced RCC previously treated with cytokines, chemotherapy, or targeted agents, axitinib provided antitumor activity with a favorable noncumulative toxicity profile. In one study of patients with cytokine-refractory mRCC, an objective response rate (ORR) of 44.2% (95% CI 30.5, 58.7) was achieved. The median time to progression was 15.7 months (95% CI 8.4, 23.4) and the median overall survival (OS) was 29.9 months (95% CI 20.3, not estimable).

In another study of patients with sorafenib-refractory mRCC, ORR was 22.6% (95% CI 12.9, 35.0). The median progression-free survival (PFS) was 7.4 months (95% CI 6.7, 11.0 months) with a median OS of 13.6 months (95% CI 8.4, 18.8).

In a third study of patients with cytokine-refractory mRCC the ORR was 55% and median PFS was 12.9 months (95% CI 9.8, 15.6).

The most common adverse events in the 3 studies were fatigue, hypertension, hand-foot syndrome (HFS), and gastrointestinal toxicity. These were generally manageable with standard medical intervention. Of note, the incidence of HFS and proteinuria in the third study was higher than that reported in the second study in cytokine-refractory mRCC patients.

An observed association between diastolic blood pressure ≥ 90 mmHg and increased efficacy suggests potential use as a prognostic biomarker. However, this requires further investigation. Two randomized phase 3 clinical trials are ongoing to determine the efficacy of axitinib in patients with mRCC as first- and second-line treatment. These results will help to determine the place of axitinib in the mRCC treatment algorithm.

Targeted Therapy Results for Xp11 Translocation RCC

Malouf GG, Camparo P, Oudard S, et al. Targeted agents in metastatic Xp11 translocation/TFE3 gene fusion renal cell carcinoma (RCC): a report from the Juvenile RCC Network. *Ann Oncol*. 2010;21:1834-1838.

Fifteen percent of patients younger than 45 years who have renal cell carcinoma (RCC) are affected with the Xp11 translocation subtype. The reserachers analyzed the benefit of targeted therapy (vascular endothelial growth factor receptor [VEGFR]-targeted agents and/or mammalian target of rapamycin [mTOR] inhibitors) in these patients.

Patients with Xp11 translocation/TFE3 fusion gene metastatic RCC who had received targeted therapy were identified. Nuclear TFE3 positivity was confirmed by reviewing pathology slides. Responses according to RECIST criteria, progression-free survival (PFS), and overall survival (OS) were analyzed.

Overall, 53 patients were identified; 23 had metastatic disease, and of these, 21 received targeted therapy (median age 34 years). Seven patients achieved an objective response. In first line, median PFS was 8.2 months (95% CI 2.6-14.7 months) for sunitinib (n = 11) versus 2 months (95% CI 0.8-3.3 months) for cytokines (n = 9; log-rank P = .003).

Further treatment (second, third, or fourth line) results were as follows: all 3 patients who received sunitinib had a partial response (median PFS 11 months). Seven of the 8 patients who received sorafenib had stable disease (median PFS 6 months). One patient who received mTOR inhibitors had a partial response, and 6 patients had stable disease. Median OS was 27 months with a 19 months median follow-up.

Study findings indicate that in Xp11 translocation RCC, targeted therapy achieved objective responses and prolonged PFS similar to those reported for clear-cell RCC.

New Cancer Genes Identified

Varela I, Tarpey P, Raine K, et al. Exome sequencing identifies frequent mutation of the SWI/SNF complex gene PBRM1 in renal carcinoma. *Nature*. 2011; 469: 539-542.

The genetics of renal cancer is dominated by the inactivation of the VHL tumor suppressor gene in clear cell carcinoma (ccRCC), the most common histological sub-

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Metastatic Renal Cell Carcinoma: Patient Characteristics, Treatment Patterns, and Schedule Compliance in Clinical Practice


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Renal cell carcinoma (RCC) represents approximately 3% of adult cancers and approximately 90% of neoplasms that originate in the kidney.[1] The majority of patients with RCC develop metastases; approximately one-third of patients present with metastatic disease.[2] It is well established that metastatic renal cell carcinoma (mRCC) is resistant to conventional chemotherapy and to radiation therapy. Until recently, treatment was limited to cytokine therapy with interleukin-2 or interferon-α.[3,4] Advances in the understanding of the biology of mRCC have contributed to the development of several new classes of molecular-targeted therapies including tyrosine kinase inhibitors (TKIs; sunitinib, sorafenib, pazopanib); an antivascular endothelial growth factor (anti-VEGF) agent (bevacizumab); and mammalian target of rapamycin signaling inhibitors (mTORs; temsirolimus, everolimus).[2]

Molecular-targeted therapies, many of which can be taken orally, have generally been associated with better efficacy and tolerability than cytokine therapy.[4-7] With the introduction of these new therapies in the past 5 years, the treatment of mRCC is undergoing a paradigm shift from predominant use of cytokine therapy to the use of molecular-targeted agents.[6] For mRCC, sequential therapy with targeted agents is the current standard of care.[8]

Keywords: Renal cell carcinoma; metastases; targeted therapy.

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Acknowledgement—This research was funded by Novartis Pharmaceuticals; it was presented at the 23rd annual meeting of the Academy of Managed Care Pharmacy; April 27-30, 2011; Minneapolis, Minnesota. The authors thank Jane Saiers, PhD, for writing assistance.

While benefits of molecular-targeted agents over cytokine therapy have been established in clinical trials, little information from real-world use of the molecular-targeted agents is available to inform their best use in clinical practice.[6,7,9] Such information is needed to elucidate the therapeutic profiles of these agents in clinical populations not subject to the restrictive inclusion and exclusion criteria of clinical trials; to define the optimal sequencing and combinations of therapy; to identify prognostic factors; and to assess adherence, which is key to optimizing outcomes with molecular-targeted therapies.[5,6,10] In addition, information from real-world clinical use of molecular-targeted agents is necessary to inform policy decisions and the development and modification of treatment guidelines, which have been rapidly evolving with the introduction of the new therapies.[5,9]

This article reviews a study that was undertaken to characterize real-world clinical use of molecular-targeted agents for mRCC. Patient characteristics, treatment patterns, and medication schedule compliance were assessed in a large cohort of newly diagnosed patients with mRCC in the United States.

Materials and Methods

Data source

Data for this retrospective, observational, cohort study were extracted from SDI's private-practice databases of longitudinal, patient-level medical and pharmacy claims collected from physicians and other health care providers across the United States. The pharmacy claims database, established in 2001, includes claims (National Council for Prescription Drug Programs [NCPDP] version 5.2) for more than 1.8 billion prescriptions dispensed annually. The medical claims database, established in 1999, includes more than 600,000 annual

claims (CMS 1500 forms). It contains diagnosis and visit information and represents activity of more than 450,000 physicians per month. Data in the databases are de-identified, and the databases are certified as being compliant with the Health Insurance Portability and Accountability Act (HIPAA). This study was exempt from institutional review board approval as it was retrospective, did not involve an intervention, and used anonymized data.

Sample

The study included male or female patients aged 18 years or older who had been newly diagnosed with mRCC (ie, having an RCC diagnosis with a concomitant or subsequent International Classification of Diseases, 9th edition [ICD-9] code for secondary neoplasm) from April 1, 2008 through February 28, 2010 (the study period) or patients previously diagnosed with RCC and newly treated with cytokine therapy, sunitinib, sorafenib, pazopanib, temsirolimus, everolimus, or bevacizumab (excluding intravitreal injection) during the study period.

Additional eligibility criteria included presence of a 90-day or longer look-back period without an mRCC diagnosis or receipt of a treatment of interest; 1 or more visits to a treating physician (defined as someone who administered chemotherapy or monoclonal antibody therapy during the study period), and presence in the dataset for 3 months or longer from first treatment, unless mortality occurred earlier. Patients with unknown age or gender; with a primary diagnosis of breast, uterine, or colon cancer or of melanoma; or with a dosing/procedure code indicative of intravitreal injection of bevacizumab for wet age-related macular degeneration; or those who received care from physicians or pharmacies without stable claims in the databases during the look-back and follow-up periods were excluded.

Data analysis

Eligible patients were indexed, using the 90-day or longer look-back period, to the first therapy postmetastasis. The index mRCC date was considered to be the first confirmed mRCC treatment date with one of the drugs of interest (cytokine therapy, sunitinib, sorafenib, pazopanib, temsirolimus, everolimus, or bevacizumab excluding intravitreal injection). The first-line regimen was considered to have ended when a 90-day gap was observed or when a drug addition/switch occurred after the first 28 days of treatment and the original regimen had been administered for at least 2 cycles. Descriptive statistics were used to summarize demographics and clinical characteristics, first-line and second-line regimens, and treatment sequences.

Schedule compliance was measured as the medication possession ratio (MPR), which was calculated as (distinct days with drug on hand)/(observed period for a line of therapy) × 100%.[11,12] For oral drugs, distinct days of drug on hand were calculated as days supply dispensed (+ 14-day grace period to the end of each sunitinib prescription). The 14-day grace period was added for sunitinib because of its usual 4-weeks-on, 2-weeks-off dosing schedule. For infused therapies, distinct days of drug on hand were calculated as administration days + duration of clinical benefit for each administration (interferon 6 days; proleukin 4 days; temsirolimus 6 days; bevacizumab 13 days). Observed period for a line of therapy was the number of days between start of a line of therapy and either end of the line or last follow-up, whichever occurred earlier. The MPR was compared between regimens using t-tests.

Table 1. Demographics and Other Characteristics

	N = 1080
Men, n (%)	737 (68.2)
Age, years	
Mean	65.9 (11.0)
Median	65.0
Region, n (%)	
Midwest	246 (22.8)
Northeast	177 (16.4)
South	383 (35.5)
West	274 (25.4)
Payer, n (%)	
Commercial	637 (59.0)
Medicare	373 (34.5)
Medicaid	35 (3.2)
Other	35 (3.2)
Physician specialty, n (%)	
Hematolgy/oncology	882 (81.7)
Internal medicine	76 (7.0)
Nephrology	2 (0.2)
Other	120 (11.1)
Physician affiliation	
Community	482 (44.6)
Affiliated with academic institution	472 (43.7)
Other	126 (11.7)
Year of mRCC initial diagnosis/treatment, n (%)	
2008	399 (36.9)
2009	642 (59.4)
2010	39 (3.6)
Patients with known sites of metastasis, n (%)	336 (31.1)
Bone	148 (13.7)
Lung	105 (9.7)
Liver	31 (2.9)
Colon/rectum	9 (0.8)
Head and neck	5 (0.5)
Brain	2 (0.2)
Skin	2 (0.2)
Bladder	2 (0.2)
Breast	1 (0.1)
Other	31 (2.9)
Charlson Comorbidity Index, mean (SD)	3.9 (2.1)

Results

Sample

The sample comprised 1080 newly treated, predominantly male patients with mRCC with a median age of 65 years (**Table 1**). Approximately 31% of patients were coded as metastatic (n = 336); bone, lung, and liver were

Table 2. Common mRCC Treatment Regimens

	Sunitinib	Temsirolimus	Bevacizumab	Interferon	Sorafenib	All others
2008-2010						
First line (N = 1080)						
n (%)	525 (48.6)	319 (29.5)	90 (8.3)	58 (5.4)	42 (3.9)	46 (4.4)
Observed days[a]						
Mean	136	121	94	48	102	146
Median	77	85	81	36	49	126
	Sunitinib	**Everolimus**	**Temsirolimus**	**Bevacizumab**	**Sorafenib**	**All others**
Second line (N = 246)						
n (%)	55 (22.4)	45 (18.3)	44 (17.9)	39 (15.9)	26 (10.6)	37 (15.1)
Observed days[a]						
Mean	94	72	106	65	78	NA
Median	48	60	56	39	37	NA
	Temsirolimus	**Sunitinib**	**Bevacizumab**	**Interferon**	**Everolimus**	**All others**
Treatment initiated in 2009						
First line (N = 711)						
n (%)	291 (40.9)	283 (39.8)	50 (7.0)	31 (4.4)	23 (3.2)	33 (4.6)
	Everolimus	**Bevacizumab**	**Sunitinib**	**Temsirolimus**	**Sorafenib**	**All others**
Second line (N = 155)						
n (%)	35 (22.6)	30 (19.4)	29 (18.7)	22 (14.2)	12 (7.7)	27 (17.4)

[a]Actual treatment durations for each agent could be longer than the observed days, which were right censored at the last follow-up date

the most common sites of metastases (**Table 1**). The remainder of patients were also considered to have metastatic disease because of the use of cytokines and/or targeted therapies. More than half of the patients (59%) had commercial insurance, and the majority (59.4%) of the patients entered the study in 2009 (first mRCC diagnosis or mRCC treatment). The average baseline Charlson Comorbidity Index (CCI) was 3.9 (standard deviation [SD] = 2.1, maximum possible CCI = 32). The majority of patients were treated by either an oncologist or a hematologist (81.7%). Approximately 43.7% of treating physicians had an affiliation with an academic institution.

Treatment patterns

The most common first-line treatments were sunitinib, temsirolimus, bevacizumab, and interferon; the most common second-line treatments were sunitinib, everolimus, temsirolimus, and bevacizumab (**Table 2**). Common first-line/second-line regimens were similar between men and women and between those who were younger than 65 years and those who were 65 years or older. For patients initiating mRCC first-line therapy in 2009, the most common first-line treatments were temsirolimus, sunitinib, bevacizumab, and interferon. The most common second-line treatments were everolimus, bevacizumab, sunitinib, and temsirolimus (**Table 2**).

Among the 246 second-line patients with mRCC, a first-line TKI (sunitinib/sorafenib) followed by second-line everolimus or sunitinib were the most common treatment sequences (**Figure 1**). Among the 155 second-line patients who initiated their first-line treatment in 2009, a first-line TKI (sunitinib/sorafenib) followed by second-line everolimus, and a first-line mTOR (temsirolimus/everolimus) followed by second-line bevacizumab were the most common treatment sequences (**Figure 1**).

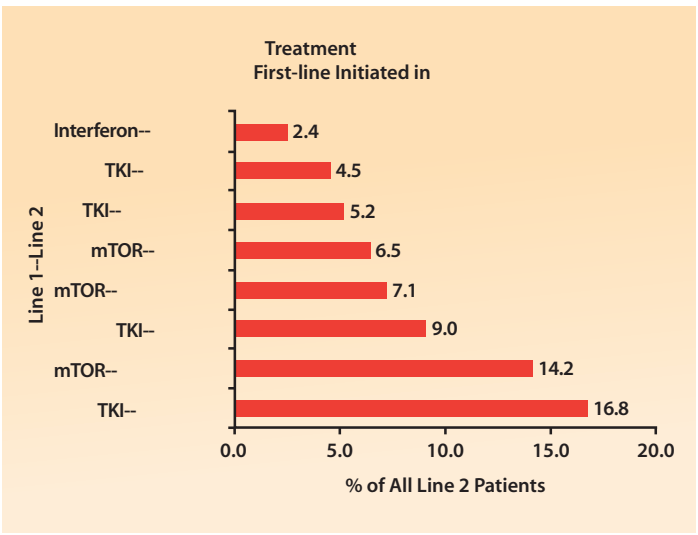

Figure 1. Common mRCC treatment sequences.

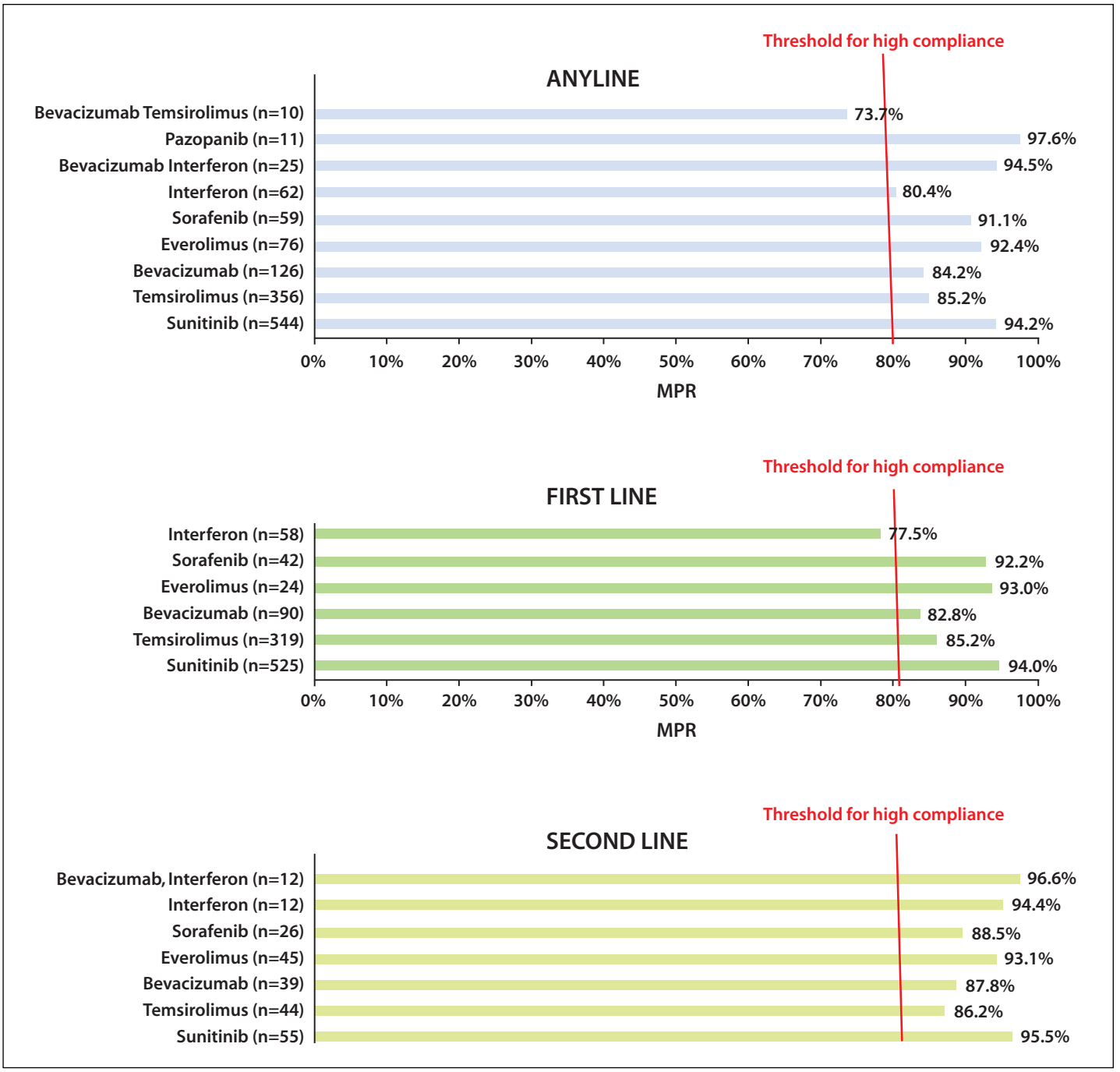

Figure 2. MPR by line of therapy.

Schedule compliance

Patients were followed on first-line therapy for a mean of 121 days and a median of 75 days and on second-line therapy for a mean of 80 days and a median of 44 days (**Figure 2**). The majority of patients (81.1%) had an MPR of 0.80 or higher, a value that reflects good compliance. Within first-line therapy, the oral therapies sunitinib and sorafenib (MPR 0.92-0.94) had significantly ($P <$ .001) higher schedule compliance than the infused therapies temsirolimus, bevacizumab, or interferon (MPR 0.78-0.85). Within second-line therapy, sunitinib (MPR 0.96), everolimus (MPR 0.93), and interferon (MPR 0.94) were statistically equivalent and were associated with significantly ($P <$ .001) higher schedule compliance than bevacizumab (MPR 0.88), sorafenib (MPR 0.89), or temsirolimus (MPR 0.86).

Sensitivity analyses

Treatment patterns remained similar when minimum follow-up period was extended from 3 months to 6 months. The results of the schedule compliance analysis with 6-month minimum follow-up period concurred with that of the primary analysis where the minimum follow-up period was 3 months—the majority of

patients still had high MPR, and within the first line of therapy, oral regimens were associated with better schedule compliance than infused regimens.

Discussion

The rapidly evolving therapeutic landscape for mRCC, with the addition of 6 new molecular-targeted treatments since 2005 in the United States, has led to calls for studies to characterize the use of and outcomes with the new therapies in real-world clinical practice.[5,9] Such information is a necessary complement to information from clinical trials in informing clinical use and policy decisions involving the new agents. The current study characterized patient characteristics, treatment patterns, and schedule compliance with molecular-targeted agents in a large, nationally representative cohort of patients with mRCC (N = 1080).

The characteristics of the identified patients with mRCC were similar to the known demography of mRCC.[1] The most common first-line treatments were sunitinib and temsirolimus, and the most common second-line treatments were sunitinib and everolimus. The most common treatment sequence was sunitinib or everolimus after a first-line TKI (sunitinib/sorafenib). These treatment patterns should be interpreted with the knowledge that the line of therapy reported in this study was based on analysis of claim activities, which might not completely reflect patients' actual drug-taking behavior. However, these treatment choices and sequences appear to reflect application of findings from clinical trials and are consistent with current treatment guidelines.[8,13]

Sunitinib and temsirolimus have been demonstrated to be superior to the cytokine interferon-α in prolonging progression-free survival and/or overall survival time[14-18]; and temsirolimus has been demonstrated to be active in patients with poor prognosis.[3] Everolimus was demonstrated to be superior to placebo plus best supportive care in a phase 3 trial of patients with mRCC refractory to VEGF receptor TKIs.[19,20]

Schedule compliance with mRCC treatments was generally high among the majority of patients: 81.1% of patients had an MPR of 0.80 or higher, a value that reflects good compliance. Within first-line therapy, schedule compliance was higher with oral treatments than with infused treatments. Within second-line therapy, sunitinib, everolimus, and interferon were associated with higher schedule compliance than other commonly used second-line agents. While better schedule compliance with oral treatments compared with infused treatments was not unexpected, the reasons for the differences in schedule compliance among individual oral molecular-targeted therapies are unknown and warrant further study.

It is important to note that schedule compliance measured how well patients refilled their prescriptions or received the infusions according to the recommended dosing schedule; whether patients actually took the drug and whether physicians instructed the patient to use a lower dose or delayed the infusion because of toxicity are unknown. Schedule compliance with molecular-targeted agents is crucial for optimizing therapy, and adequate exposure to targeted agents is associated with greater probability of improved survival.[10] Differences in schedule compliance among targeted agents may have an effect on therapeutic outcome. However, the MPRs reported here only reflect patient schedule compliance during the therapy period while they were observed.

The results of this study should be interpreted in the context of limitations of the study. Claims data can be inherently limiting because they are collected for billing and reimbursement purposes rather than for research purposes. Therefore, claims data often lack information that could be important to the research question at hand. For example, information on histology and prior nephrectomy was not available for this study. In addition, data entry errors at the site of care could not be corrected for in data analysis.

The retrospective, observational nature of the study also should be borne in mind in interpreting the results. Retrospective analyses demonstrate associations but do not indicate causality. Furthermore, the retrospective, observational nature of the study could make the results subject to selection bias. Finally, in this rapidly evolving era of molecular-targeted therapy of mRCC, results should be interpreted with awareness of the time frame in which the study was conducted. The data from this investigation can be considered complementary to other analyses that may assess populations that differ from the current one on dimensions such as payer influences or geographic region or that differ in methods of data capture or analysis.

Conclusion

This study provides new information about contemporary, real-world use of molecular-targeted therapies and cytokine therapy in a large, nationally representative sample of patients with mRCC in the United States.

- The most common first-line treatments were sunitinib and temsirolimus; the most common second-line treatments were sunitinib and everolimus.
- The most common treatment sequence was a TKI (sunitinib/sorafenib) followed by sunitinib or everolimus.
- Schedule compliance with the new molecular-targeted therapies was generally high with better schedule compliance rates with oral therapy than infused therapy during first-line therapy and better schedule compliance rates with sunitinib, everolimus, and interferon than other commonly used agents during second-line therapy. The schedule compliance results in particular warrant confirmation and further study in other treatment settings and mRCC patient populations.

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GUEST EDITOR'S MEMO

(continued from page 80)

advanced disease at time of nephrectomy and they are at greater risk of death
from RCC compared with never smokers.

We know more precisely how cigarette smoking is an independent risk factor for advanced RCC. Higher intensity, longer duration of smoking, and greater cumulative exposure are associated with a probable increase in advanced disease (ie, worse prognosis at presentation and more negative patient outcomes). The risk for RCC decreases with the longer duration of durable smoking cessation, therefore smoking cessation may be the single most effective measure to slow progression of disease.

Bernard Escudier, MD
Guest Editor
Editor-in-Chief

Cigarette Smoking and Renal Cell Carcinoma

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The National Cancer Institute estimates that there will be 60,920 new cases of kidney cancer in the United States in 2011, and there will be a resulting 13,120 deaths.[1] According to the American Cancer Society, kidney cancer is the fifth most common cancer overall.[2] In the past 3 decades, the prevalence of renal cancer has been increasing steadily each year in the United States and Europe.

The association between cigarette smoking and cardiovascular and pulmonary diseases as well as numerous cancers has long been established. In the United States, smoking is indicated as the causative factor in 90% of lung cancer deaths in men and approximately 80% of lung cancer deaths in women.[3] With the steadily increasing incidence of renal cell carcinoma (RCC) in recent years, more attention has been dedicated to the study of risk factors for this cancer in the attempt to gain insight on mechanisms of disease and potential strategies of prevention.

The risk factors associated with RCC include male gender, older age, renal insufficiency, cigarette smoking, hypertension, obesity, physical inactivity, and diabetes. Of note, cigarette smoking is among the few modifiable risk factors.[4] Although cigarette smoking is a recognized risk factor for RCC, little data are available on the association between smoking history (ie, duration, intensity, cessation) and tumor characteristics and outcomes and the potential mechanisms are still poorly understood.[5]

More recent findings suggest that smoking is one of the most important risk factors for RCC. This is particularly true for patients with pre-existing renal disease and elderly men with hypertension. Furthermore, smoking may impair renal function in patients with apparently healthy kidneys and thus contribute to the risk of cancer.[6]

In this article we review and summarize the data regarding the aspects of smoking that may be associated with RCC incidence and characteristics.

Keywords: Renal cell carcinoma; cigarette smoking; hypertension.

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Suspected Mechanisms

Cigarettes smoke contains more that 45,000 chemicals (eg, nicotine, tar, ammonia, carbon monoxide, carbon dioxide, formaldehyde, acrolein, acetone, benzopyrenes, hydroxyquinone, nitrogen oxides, cadmium) many of which are known to be carcinogenic.[7] This extreme range of potentially implicated toxic substances makes it difficult to attribute a specific substance key role in carcinogenesis. However, general mechanisms have been proposed and the role of nicotine has been extensively studied.

These toxins can increase cell turnover and induce DNA damage, which may be involved in carcinogenesis and cancer progression. In addition, cigarette smoking has been shown to be associated with a myriad of genetic and epigenetic abnormalities such as gene mutation, deletions, and DNA methylation. Furthermore, smoking may promote an inflammatory state by creating a relatively hypoxic environment, and it may suppress immune response. The combination of the above listed effects could facilitate emerging neoplastic clones by providing them an adequate environment, furthermore, suppression of immune system control removes part of the regulation of cell proliferation and proinflammatory and angiogenic effects actively support the neoplastic process.

The Role of Nicotine

The proangiogenic effects of nicotine may promote tumor growth. Nicotine has been shown to stimulate endothelial cell tube formation via pathways mediated by the angiogenic growth factors such as basic fibroblast growth factor (bFGF) or vascular endothelial growth factor (VEGF). Nicotine was shown to induce bFGF but not VEGF release from human endothelial cells. Nicotine effectively promoted the generation of new blood vessels from existing ones in a chorioallantoic membrane (CAM) model, and doubled tumor growth in the CAM

tumor implant model regardless of the tumor type indicating nontumor-specific promotion of growth via shared angiogenetic pathways.[8]

Nicotine has been shown to induce angiogenesis in a number of other models. In a study by Heeschen and colleagues,[9] tumor growth was markedly accelerated in the nicotine group and corresponded with increased vascularization of the tumor tissue. The researchers observed significantly higher capillary density in the tumors from mice exposed to nicotine 1.1 (95% CI 0.8-1.7) versus 0.2 (0.1-0.4) capillaries/kilopixel; $P < .001$. In another experiment, Lewis lung cancer cells were orthotopically implanted into the animal lung parenchyma. Tumor vascularization was again significantly higher in the nicotine group: 1.8 capillaries/kilopixel (95% CI 0.9-2.5) versus 0.5 capillaries/kilopixel (95% CI 0.2-0.9); $P < .001$. The systemic levels of VEGF were also significantly higher in the nicotine group compared with controls: 54.1 (95% CI 170.0-225.7) pg/mL; $P < .001$.

Another interesting aspect is that nicotine increases sympathetic activity via direct stimulation of postganglionic sympathetic nerve endings. Smoking a single cigarette markedly increases plasma concentration of norepinephrine and epinephrine in healthy volunteers, whereas postganglionic muscle sympathetic nerve traffic decreases significantly. Thus, nicotine triggers catecholamine release from peripheral sympathetic nerve endings and the adrenal medulla. This increased sympathetic activity may represent yet another mechanism involved.[6]

Nicotine is only one of the numerous substances contained in cigarette smoke. The extensive research into nicotine's effect, however, shows that a variety of pathways and molecular mechanisms may be of importance with regard to renal carcinogenesis.

Smoking and Hypertension

Smoking is an especially high renal risk factor in hypertensive patients. The exact mechanisms have not yet been elucidated, although increase in blood pressure, alteration of intrarenal hemodynamics, as well as activation of the sympathetic nerve, the renin-angiotensin, and the endothelin systems could represent potential mechanisms of smoking-induced renal damage. In patients with primary hypertension proteinuria has been found in 4% to 18% of patients and albuminuria in 10% to 25% of patients and smoking increased this risk.[10]

Hörner and colleagues[11] found that smoking was the strongest predictor for albuminuria in patients with primary hypertension. Halimi and colleagues[12] reported on results from a study that included 28,409 subjects. Their findings show an increased risk of irreversible proteinuria that may occur despite moderate smoking. Hypertension and functional damage to the kidney may play a concerted role in forming the ground for renal carcinogenesis. The notion that smoking effects may be more pronounced in men and the elderly[6] is in line with male predominance and older age association of RCC, , which suggests intricate relationships between the different risk factors.

Current Smokers Versus Past Smokers Versus Never Smokers

Although there is considerable evidence for the link between cigarette smoking and increased risk of RCC, the results of a meta-analysis showed that the association between RCC risk and the duration of smoking is not as well established. The results from a study by Theis and colleagues[13] showed that relative risk (RR) for RCC in smokers (current or past) was 1.38, and the risk was greater in men (RR = 1.50) than in women (RR = 1.27).[5] When exposure was measured in pack-years, trends between RCC and smoking were stronger ($P = .014$). There was a 30% risk increase of RCC in smokers compared with never smokers. Moreover, the association was greater when smokers of 20 or more pack-years were compared with those of less than 20 pack-years, which suggests a dose-dependent effect of cigarette smoking on the risk of RCC.

While cigarette smoking is a risk factor, smoking cessation appears to reverse this association. Theis and colleagues,[13] in a population-based study, found a trend of decreasing risk across 10-year smoking cessation intervals: those who had stopped smoking 11 to 20 years earlier had a 60% decrease in risk compared with current smokers.[13]

A drop in relative risk of RCC in long-term former smokers compared with patients who had recently stopped smoking was also reported by Hunt and colleagues.[14] However, the results of their meta-analysis were not conclusive because of significant heterogeneity in the methods used to determine the length of smoking cessation in the evaluated studies.

Findings from a population-based case-control study suggest that long-term smoking cessation (20 or more years) reduces the risk of RCC to a level that is equal to that of never-smokers, even after adjustment for lifetime smoking intensity and duration. Shorter cessation periods (<10 years, 10 to 19 years) were associated with only moderate reductions in RCC risk. Multivariate adjustment for other risk factors for RCC did not alter the results. There was no evidence that showed that risk reduction associated with smoking cessation differed according to gender, BMI, or pack-years of smoking.[15]

Our group looked at the association between cigarette smoking and smoking cessation and RCC stage among patients undergoing surgery.[16] In this large cohort of multiethnic patients, 207 (24.5%) had advanced disease and 638 (75.5%) had localized tumors. There were more men in the former and current smoker groups ($P < .001$). Advanced RCC was more frequent in former and current smokers (29.3% and 28.7%, respectively) compared with nonsmokers (20.2%; P = .012). Locally advanced disease (stage T3 or higher) was found in 16.3% of never smokers compared with 25.7% in current

and past smokers. After adjusting for covariates (age, ethnicity, sex, and personal and family history of cancer) cigarette smoking was still significantly associated with advanced RCC, which reinforces the importance of smoking as a risk factor not only for RCC but also specifically for pathological characteristics of kidney cancer portending worse prognosis. Moreover, in this study the deleterious associations were, at least in part, reversed by smoking cessation with long-term quitters approximating the risk of advanced disease of never smokers.

RCC Outcomes

Cigarette smoking may be associated with worse prognosis and higher disease-specific mortality for RCC. Parker and colleagues[17] reported on 392 (17.5%) current cigarette smokers, 762 (34.0%) former smokers, and 1088 (48.5%) never smokers undergoing surgery for RCC. While their results were similar to our study results[16] there were differences in disease stage at presentation, namely, current smokers were more likely to be symptomatic, have regional lymph node involvement (8% vs 4% and 5%; $P = .024$) and distant metastases (22% vs 13% and 135%; $P < .001$) as well as TNM stage IV disease (24% vs 14% and 15%; $P = .002$) compared with former and never smokers. Analyzing survival of these patients following surgery, the authors found that current smokers were 31% more likely to die from RCC compared with never smokers. However, after adjusting for TNM stage and nuclear grade, the association with current cigarette smoking was no longer apparent, suggesting that disease characteristics in smokers were likely responsible for the worse outcomes.[17]

As reported by Colli and associates,[18] smoking, obesity, hypertension and physical inactivity are directly associated with RCC incidence. Moreover, smoking, obesity and physical inactivity were reportedly correlated to RCC mortality. These findings emphasize the importance of smoking as a risk factor beyond cardiovascular disease and indicate the potential impact of smoking on tumor features that denote more aggressive phenotype with consequent worse prognosis and higher disease-specific mortality rates.

Differences in Gender

Recent data indicate that men may be more susceptible to smoking-induced renal damage than women. The results of a population-based, cross-sectional study of 11,247 adults showed that smoking was independently associated with renal impairment in men (odds ratio [OR] = 3.59) but not in women.[19] Gender-dependent effects, shown for renal functional damage, appear to be consistent for renal carcinogenesis as well.

Flaherty and colleagues[20] studied the association between hypertension, thiazide use, body mass index, weight change, and smoking and risk of RCC in 2 large cohorts: the Nurses' Health Study and the Health Professionals Follow-up Study. Their findings indicate that the risk associated with smoking may have different magnitudes among men and women. The results of the study also show a clear dose-response with pack-years of smoking in men, but not in women. Although smoking as a risk factor for RCC is listed as a consistent factor by both the International Agency for Research on Cancer and the US Surgeon General, data from the study by Flaherty and colleagues[20] suggest different magnitudes of this association across genders. This intriguing finding should be explored further to elucidate the differential pathways that may help in understanding the molecular mechanisms behind smoking-induced renal damage and carcinogenesis.

Summary

Cigarette smoking continues to be the leading cause of preventable morbidity and mortality in the United States.[21] It is responsible for nearly 20% of all deaths each year.[22] Tumors of the urinary bladder, larynx, esophagus, colon and rectum, and kidney have all been linked to cigarette smoking.

The evidence is clear that cigarette smoking contributes significantly to the increased risk of RCC. Smoking intensity, duration and total exposure are associated with increased risk of RCC. There is evidence that smoking cessation may revert this association and, with durable smoking cessation, bring the risk of kidney cancer to that of never smokers.

Smoking cessation should be emphasized not only for prevention of cardiovascular and pulmonary diseases but also because of the consequences of smoking on renal function and kidney carcinogenesis. In fact, cigarette smoking is one of the modifiable risk factors for RCC that can be acted upon on personal and population levels. As such, the adoption of smoking prevention cessation strategies should be encouraged.

In conclusion, cigarette smoking is an independent risk factor for RCC. Higher intensity, longer duration of smoking, and greater cumulative exposure are associated with an increase in the risk of RCC and specifically, advanced disease that portends worse prognosis. Smoking cessation has been shown to reduce these associations. Despite suggestions of gender-dependent effects of smoking on RCC risk, smoking cessation benefits are seen across genders. Given the established link between cigarette smoking and RCC, the importance of smoking cessation should be reinforced. Despite accumulating data, there are still unfilled gaps in our understanding of the pathways involved and more detailed connections between smoking and RCC. Specifically, it has been suggested that smokers are at increased risk of RCC-specific mortality, and presentation at advanced stage. It may be that smoking, and compounds contained in cigarette smoke, fuel cancer growth via proinflammatory and proangiogenetic effects. However, more research is needed to elucidate the effects of smoking and its cessation on RCC outcomes and prognosis, as well as to help in understanding the mechanisms that result in a more aggressive RCC phenotype in smokers.

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MEDICAL INTELLIGENCE

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phisms (SNPs) in VEGF pathway and genes with PFS and blood pressure (BP)-related endpoints.

DNA samples (n = 263, 36% of patients) from blood were genotyped using Taqman allelic discrimination. Potential associations between SNPs in VEGF pathway genes (*VEGF-A*, *VEGFR1*, *VEGFR2*, *HIF1*) and PFS were evaluated in the white subpopulation only (n = 249), as well as between SNPs in *VEGF-A*, VEGFR1, and *VEGFR2* with hypertension (Grade 3 or greater) and high BP (at least one diastolic BP [dBP] reading of $\geq$ 90 mmHg).

Differences in PFS were seen with *VEGF-A* SNPs rs1570360 (adjusted $P = .127$; Cox regression interaction test), rs699947 ($P = .058$), and rs833061 ($P = .058$). Log-rank tests indicated that potential associations between PFS and genotype for these 3 SNPs are driven more by differences in PFS among genotypes in the axitinib arm than in the sorafenib arm. For example, the median PFS for *VEGF-A* rs699947 A/A in axitinib-treated patients was 52 weeks (vs 28 weeks for other genotypes; adjusted $P = .16$), while no difference in PFS among these genotypes was noted in sorafenib-treated patients (adjusted $P = .95$). After adjusting for multiple testing, no statistically significant correlations were observed between SNPs and hypertension or high dBP using logistic regression analysis.

Three *VEGF-A* SNPs were potentially associated with PFS. None of the VEGF pathway SNPs examined was associated with axitinib-related hypertension or dBP. These results support previously reported associations of rs1570360 and rs699947 with overall survival in a trial of a bevacizumab-based regimen (Schneider et al. *J Clin Oncol*. 2008;26:4672), and association of germline SNPs with efficacy for pazopanib (Xu et al. *ASCO GU*. 2011:303). These exploratory data suggest that specific SNPs might help to explain some of the observed interpatient variability in PFS for the RCC patients who received axitinib therapy. Moreover, germline SNPs might be important tools in the future to guide selection of VEGF

Abstract 1006

Motzer RJ, Escudier B, Bukowski R, et al. Prognostic Factors for Progression-Free Survival, Overall Survival), and Long-Term Overall Survival With Sunitinib in 1059 Patients, Treated on Clinical Trials, With Metastatic Renal Cell Carcinoma

With the advent of multiple targeted therapies for metastatic renal cell carcinoma (mRCC), further information on factors that affect prognosis facilitates both clinical decision making and trial design for evaluation of new therapies. The researchers report on a retrospective analysis of prognostic factors for progression-free survival (PFS), overall survival (OS) and long-term overvall survival (LT-OS) of at least 30 months in patients with mRCC treated with sunitinib in 6 clinical trials (NCT00054886, NCT00077974, NCT00083889, NCT00338884, NCT00137423, NCT00267748; Pfizer).

Analyses used pooled data from 1059 patients treated with single-agent sunitinib on the approved 50 mg/day 4-week-on/2-week-off schedule (n = 689; 65%) or 37.5 mg continuous once-daily dosing (n = 370; 35%), in the first-

(n = 783; 74%) or second-line (n = 276; 26%) setting. Baseline variables were analyzed for prognostic significance using a Cox proportional hazards model, with each factor investigated in univariate and then multivariate analyses using a stepwise algorithm.

Multivariate analysis of PFS and OS identified 9 and 10 independent predictors, respectively (**Table,** below). Overall, 215 patients (20%) survived at least 30 months. An analysis of baseline characteristics of these long-term survivors showed differences between these patients and non–long-term survivors, including risk status based on the published Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic criteria (Motzer, 2002; $P < .0001$). For example, 70% of the long-term survivors had favorable risk features compared with 31% of non–long-term survivors. In contrast, 42% and 5% of the non–long-term survivors had intermediate and poor risk features compared with 28% and 0% of long-term survivors, respectively. Additional characteristics associated with LT-OS will be presented.

These analyses validated use of clinical risk factors previously reported from MSKCC (*J Clin Oncol*. 2002;20:286) and by Heng and colleagues (*J Clin Oncol*. 2009;27:5794). These factors were predictive for shorter PFS as well. In addition, patients with bone metastases had shorter OS to sunitinib. Favorable MSKCC risk status was associated with higher likelihood of achieving LT-OS. Continued progress requires incorporation of RCC tumor-specific biology. KCJ

Variable	PFS HR (95% CI)	*P*-value[a]	OS HR (95% CI)	*P*-value[a]
Ethnic origin (white vs non-white)	0.598 (0.459, 0.781)	.0002	0.730 (0.535, 0.996) .	0474
ECOG PS[b] (≥ 1 vs 0)	1.250 (1.043, 1.498)	.0159	1.505 (1.218, 1.859)	.0002
Time from diagnosis to treatment[†] (≥1 vs <1 year)	0.814 (0.680, 0.975) .	0252	0.666 (0.541, 0.820)	.0001
Bone metastases (yes vs no)	-	-	1.535 (1.250, 1.886)	< .0001
Baseline hemoglobin[b] (≤ LLN vs > LLN)	1.384 (1.144, 1.675)	.0008	1.548 (1.245, 1.925)	< .0001
Baseline lactate dehydrogenase[b] (> 1.5xULN vs ≤ 1.5xULN)	1.664 (1.201, 2.305)	.0022	1.571 (1.103, 2.238)	.0123
Baseline corrected calcium[b] (> 10 vs ≤ 10 mg/dL)	1.374 (1.080, 1.747)	.0096	2.208 (1.722, 2.832)	< .0001
Baseline neutrophils (≤ ULN vs > ULN)	0.629 (0.483, 0.821)	.0006	0.681 (0.508, 0.915)	.0107
Baseline platelets (≤ ULN vs > ULN)	0.607 (0.469, 0.785)	.0001	0.670 (0.505, 0.889)	.0055
Prior cytokine (yes vs no)	1.342 (1.085, 1.659)	.0066	1.387 (1.094, 1.759)	.0068

[a]Wald Chi-Square Test; [b]Factor included in MSKCC prognostic model.

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type. A recent large-scale screen of 3500 genes by PCR-based exon resequencing identified several new cancer genes in ccRCC including *UTX* (ie, *KDM6A*), *JARID1C* (ie, *KDM5C*), and *SETD2*. These genes encode enzymes that demethylate (*UTX*, *JARID1C*) or methylate (*SETD2*) key lysine residues of histone H3. Modification of the methylation state of these lysine residues of histone H3 regulates chromatin structure and is implicated in transcriptional control. However, these mutations are present in fewer than 15% of ccRCC, which suggests the existence of additional, currently unidentified cancer genes.

Varela and colleagues sequenced the protein coding exome in a series of primary ccRCC and identified the SWI/SNF chromatin remodelling complex gene *PBRM1* as a second major ccRCC cancer gene, with truncating mutations in 41% (92/227) of cases. These data further elucidate the somatic genetic architecture of ccRCC and emphasize the marked contribution of aberrant chromatin biology.

A Biomarker for Efficacy

Rini BI, Cohen DP, Lu DR, et al. Hypertension as a biomarker of efficacy in patients with metastatic renal cell carcinoma treated with sunitinib. *J Natl Cancer Inst*. 2011;103:763-773.

Hypertension (HTN) is an on-target effect of the vascular endothelial growth factor pathway inhibitor, sunitinib. Rini and colleagues evaluated the association of sunitinib-induced HTN with antitumor efficacy and HTN-associated adverse effects in patients with metastatic renal cell carcinoma (mRCC).

The retrospective analysis included pooled efficacy (n = 544) and safety (n = 4917) data from 4 studies of patients with mRCC who were treated with 50-mg sunitinib daily, administered on a 4-week-on 2-week-off schedule. Blood pressure (BP) was measured in the clinic on days 1 and 28 of each 6-week cycle. Progression-free survival (PFS) and overall survival (OS) were estimated using Kaplan-Meier analysis; hazard ratios (HRs) for survival were also estimated by Cox proportional hazards analysis using HTN as a time-dependent covariate. Efficacy outcomes were compared between patients with and without HTN (maximum systolic BP [SBP] ≥ 140 mmHg or diastolic BP [DBP] ≥ 90 mmHg). Adverse effects were also compared between patients with and without HTN (mean SBP ≥ 140 mmHg or mean DBP ≥ 90 mmHg). All *P* values were 2-sided.

Patients with mRCC and sunitinib-induced HTN defined by maximum SBP had better outcomes than those without treatment-induced HTN (objective response rate: 54.8% vs 8.7%; median PFS: 12.5 months, 95% CI = 10.9 to 13.7 vs 2.5 months, 95% CI = 2.3 to 3.8 months; and OS: 30.9 months, 95% CI = 27.9 to 33.7 vs 7.2 months, 95% CI = 5.6 to 10.7 months; $P < .001$ for all). Similar results were obtained when patients were compared with vs without sunitinib-induced HTN defined by maximum DBP. In a Cox proportional hazards model using HTN as a time-dependent covariate, PFS (HR of disease progression or death = .603, 95% CI = .451 to .805; $P < .001$) and OS (HR of death = .332, 95% CI = .252 to .436; $P < .001$) were improved in patients with treatment-induced HTN defined by maximum SBP; OS (HR of death = .585, 95% CI = .463 to .740; $P < .001$) was improved in patients with treatment-induced HTN defined by maximum DBP, but PFS was not.

Few any-cause cardiovascular, cerebrovascular, ocular, and renal adverse effects were observed. Rates of adverse effects were similar between patients with and without HTN defined by mean SBP; however, hypertensive patients had somewhat more renal adverse effects (5% vs 3%; $P = .013$).

In patients with mRCC, sunitinib-associated HTN was found to be associated with improved clinical outcomes without clinically significant increases in HTN-associated adverse events. These findings support its viability as an efficacy biomarker. KCJ

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