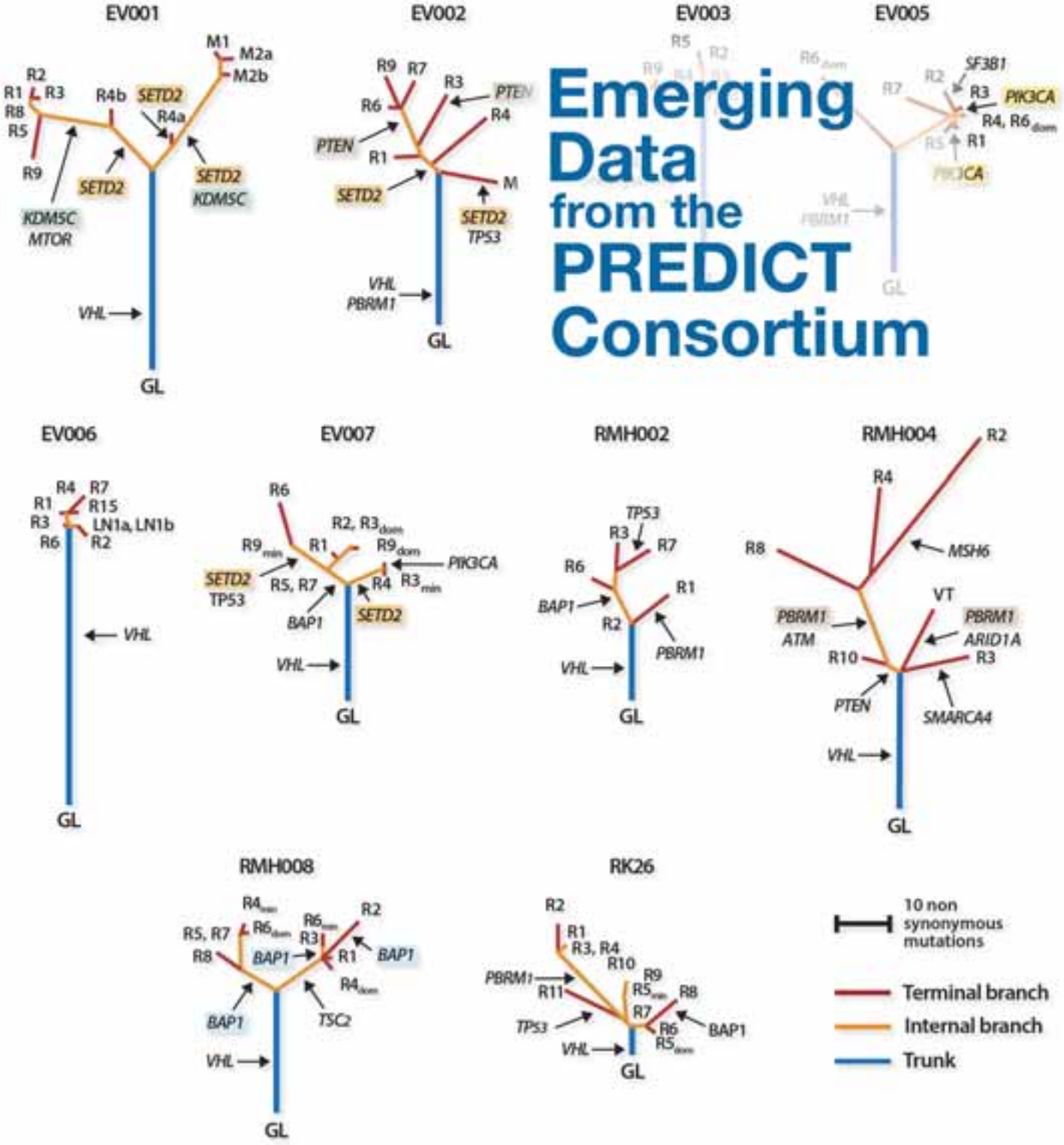
Volume 12, Number 4 Winter 2014

Kidney Cancer JOURNAL

Official Journal of The Kidney Cancer Association

kidney-cancer-journal.com

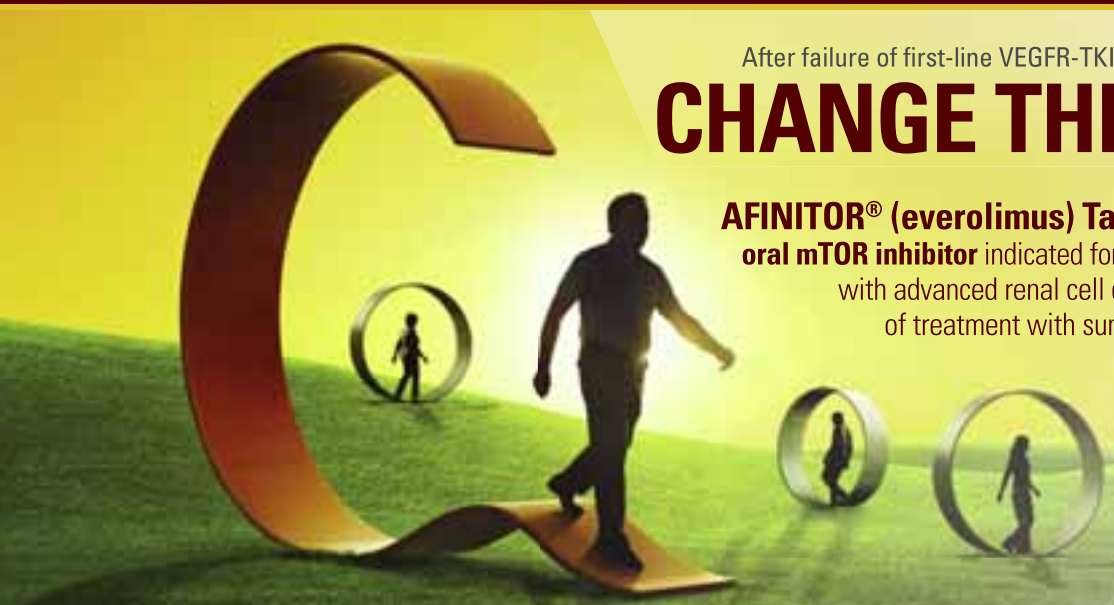
Emerging Data from the PREDICT Consortium



After failure of first-line VEGFR-TKIs sunitinib or sorafenib in aRCC,

CHANGE THEIR COURSE

AFINITOR® (everolimus) Tablets is the first and only oral mTOR inhibitor indicated for the treatment of adult patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib



Abbreviations: aRCC, advanced renal cell carcinoma; BSC, best supportive care; mTOR, mammalian target of rapamycin; PFS, progression-free survival; VEGFR-TKI, vascular endothelial growth factor receptor-tyrosine kinase inhibitor.

Proven experience[1]

- AFINITOR is now approved in 5 indications, with experience in aRCC
- A safety profile based on data in 274 patients with aRCC

3x antitumor effect[1-3]

- AFINITOR inhibits angiogenesis, growth and proliferation, and metabolism in in vitro and/or in vivo studies

More than 2x median PFS[1,4*]

- AFINITOR (n=277): 4.9 months (95% CI, 4.0-5.5); placebo (n=139): 1.9 months (95% CI, 1.8-1.9) (HR=0.33; 95% CI, 0.25-0.43; log-rank $P<0.0001$)

*In the RECORD-1 trial, AFINITOR + BSC (n=277) extended PFS vs placebo + BSC (n=139) after progression on sunitinib or sorafenib (4.9 months [95% CI, 4.0-5.5] vs 1.9 months [95% CI, 1.8-1.9]; log-rank $P<0.0001$).[1,4]

Important Safety Information

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

Noninfectious Pneumonitis:

- Noninfectious pneumonitis was reported in up to 19% of patients treated with AFINITOR. The incidence of Common Terminology Criteria (CTC) grade 3 and 4 noninfectious pneumonitis was up to 4.0% and up to 0.2%, respectively. Fatal outcomes have been observed
- Monitor for clinical symptoms or radiological changes
- Opportunistic infections such as pneumocystis jiroveci pneumonia (PJP) should be considered in the differential diagnosis
- Manage noninfectious pneumonitis by dose reduction or discontinuation until symptoms resolve, and consider the use of corticosteroids
- For patients who require use of corticosteroids, prophylaxis for PJP may be considered
- The development of pneumonitis has been reported even at a reduced dose

Infections:

- AFINITOR has immunosuppressive properties and may predispose patients to bacterial, fungal, viral, or protozoal infections (including those with opportunistic pathogens)
- Localized and systemic infections, including pneumonia, mycobacterial infections, other bacterial infections; invasive fungal infections such as aspergillosis, candidiasis, or PJP; and viral infections, including reactivation of hepatitis B virus, have occurred
- Some of these infections have been severe (eg, leading to sepsis, respiratory failure, or hepatic failure) or fatal
- Physicians and patients should be aware of the increased risk of infection with AFINITOR
- Treatment of preexisting invasive fungal infections should be completed prior to starting treatment with AFINITOR
- Be vigilant for signs and symptoms of infection and institute appropriate treatment promptly; interruption or discontinuation of AFINITOR should be considered
- Discontinue AFINITOR if invasive systemic fungal infection is diagnosed and institute appropriate antifungal treatment
- PJP has been reported in patients who received everolimus, sometimes with a fatal outcome. This may be associated with concomitant use of corticosteroids or other immunosuppressive agents; consider prophylaxis for PJP when concomitant use of these agents is required

Continued on next page

Important Safety Information (cont)

Oral Ulceration:
- Mouth ulcers, stomatitis, and oral mucositis have occurred in patients treated with AFINITOR at an incidence ranging from 44% to 78% across the clinical trial experience. Grade 3/4 stomatitis was reported in 4% to 9% of patients
- In such cases, topical treatments are recommended, but alcohol-, hydrogen peroxide-, iodine-, or thyme-containing mouthwashes should be avoided
- Antifungal agents should not be used unless fungal infection has been diagnosed

Renal Failure:
- Cases of renal failure (including acute renal failure), some with a fatal outcome, have been observed in patients treated with AFINITOR

Impaired Wound Healing:
- Everolimus delays wound healing and increases the occurrence of wound-related complications like wound dehiscence, wound infection, incisional hernia, lymphocele, and seroma
- These wound-related complications may require surgical intervention. Exercise caution with the use of AFINITOR in the perisurgical period

Laboratory Tests and Monitoring:
- Elevations of serum creatinine and proteinuria have been reported. Renal function (including measurement of blood urea nitrogen, urinary protein, or serum creatinine) should be evaluated prior to treatment and periodically thereafter, particularly in patients who have additional risk factors that may further impair renal function
- Hyperglycemia, hyperlipidemia, and hypertriglyceridemia have been reported. Blood glucose and lipids should be evaluated prior to treatment and periodically thereafter. More frequent monitoring is recommended when AFINITOR is coadministered with other drugs that may induce hyperglycemia. Management with appropriate medical therapy is recommended. When possible, optimal glucose and lipid control should be achieved before starting a patient on AFINITOR
- Reductions in hemoglobin, lymphocytes, neutrophils, and platelets have been reported. Monitoring of complete blood count is recommended prior to treatment and periodically thereafter

Drug-Drug Interactions:
- Avoid coadministration with strong CYP3A4/PgP inhibitors (eg, ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole)
- Use caution and reduce the AFINITOR dose to 2.5 mg daily if coadministration with a moderate CYP3A4/PgP inhibitor is required (eg, amprenavir, fosamprenavir, aprepitant, erythromycin, fluconazole, verapamil, diltiazem)
- Avoid coadministration with strong CYP3A4/PgP inducers (eg, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital); however, if coadministration is required, consider doubling the daily dose of AFINITOR using increments of 5 mg or less

Hepatic Impairment:
- Exposure to everolimus was increased in patients with hepatic impairment
- For patients with severe hepatic impairment (Child-Pugh class C), AFINITOR may be used at a reduced dose if the desired benefit outweighs the risk. For patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment, a dose reduction is recommended

Vaccinations:
- The use of live vaccines and close contact with those who have received live vaccines should be avoided during treatment with AFINITOR

Embryo-Fetal Toxicity:
- Fetal harm can occur if AFINITOR is administered to a pregnant woman
- Advise female patients of reproductive potential to use highly effective contraception while using AFINITOR and for up to 8 weeks after ending treatment

Adverse Reactions:
- The most common adverse reactions (incidence ≥30%) were stomatitis (44%), infections (37%), asthenia (33%), fatigue (31%), cough (30%), and diarrhea (30%)
- The most common grade 3/4 adverse reactions (incidence ≥5%) were infections (10%), dyspnea (7%), stomatitis (5%), and fatigue (5%)

Laboratory Abnormalities:
- The most common laboratory abnormalities (incidence ≥50%, all grades) were: decreased hemoglobin (92%) and lymphocytes (51%); and increased cholesterol (77%), triglycerides (73%), glucose (57%), and creatinine (50%)
- The most common grade 3/4 laboratory abnormalities (incidence ≥5%) were decreased hemoglobin (13%), lymphocytes (18%), and phosphate (6%), and increased glucose (16%)

Please see Brief Summary of Prescribing Information on adjacent pages.

References: 1. AFINITOR [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2014. **2.** Yuan R, Kay A, Berg W, Lebwohl D. Targeting tumorigenesis: development and use of mTOR inhibitors in cancer therapy. *J Hematol Oncol.* 2009;2:45. **3.** Dancey JE. Inhibitors of the mammalian target of rapamycin. *Expert Opin Investig Drugs.* 2005;14:313-328. **4.** Motzer RJ, Escudier B, Oudard S, et al. Phase 3 trial of everolimus for metastatic renal cell carcinoma: final results and analysis of prognostic factors. *Cancer.* 2010;116(18):4256-4265.

NOVARTIS ONCOLOGY

AFINITOR® (everolimus) tablets 2.5mg | 5mg | 7.5mg | 10mg

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

8/14 AFI-1095434

AFINITOR® (everolimus) tablets for oral administration
AFINITOR® DISPERZ (everolimus tablets for oral suspension)
Initial U.S. Approval: 2009

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

1 INDICATIONS AND USAGE

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Non-infectious Pneumonitis

Non-infectious pneumonitis is a class effect of rapamycin derivatives, including AFINITOR. Non-infectious pneumonitis was reported in up to 19% of patients treated with AFINITOR in clinical trials. The incidence of Common Terminology Criteria (CTC) Grade 3 and 4 non-infectious pneumonitis was up to 4.0% and up to 0.2%, respectively *[see Adverse Reactions (6.1, 6.2, 6.3, 6.4, 6.5) in the full prescribing information]*. Fatal outcomes have been observed.

Consider a diagnosis of non-infectious pneumonitis in patients presenting with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough, or dyspnea, and in whom infectious, neoplastic, and other causes have been excluded by means of appropriate investigations. Opportunistic infections such as pneumocystis jiroveci pneumonia (PJP) should be considered in the differential diagnosis. Advise patients to report promptly any new or worsening respiratory symptoms.

Patients who develop radiological changes suggestive of non-infectious pneumonitis and have few or no symptoms may continue AFINITOR therapy without dose alteration. Imaging appears to overestimate the incidence of clinical pneumonitis.

If symptoms are moderate, consider interrupting therapy until symptoms improve. The use of corticosteroids may be indicated. AFINITOR may be reintroduced at a daily dose approximately 50% lower than the dose previously administered *[see Table 1 in Dosage and Administration (2.2) in the full prescribing information]*.

For cases of Grade 3 non-infectious pneumonitis interrupt AFINITOR until resolution to less than or equal to Grade 1. AFINITOR may be re-introduced at a daily dose approximately 50% lower than the dose previously administered depending on the individual clinical circumstances *[see Dosage and Administration (2.2) in the full prescribing information]*. If toxicity recurs at Grade 3, consider discontinuation of AFINITOR. For cases of Grade 4 non-infectious pneumonitis, discontinue AFINITOR. Corticosteroids may be indicated until clinical symptoms resolve. For patients who require use of corticosteroids for treatment of non-infectious pneumonitis, prophylaxis for PJP may be considered. The development of pneumonitis has been reported even at a reduced dose.

5.2 Infections

AFINITOR has immunosuppressive properties and may predispose patients to bacterial, fungal, viral, or protozoal infections, including infections with opportunistic pathogens *[see Adverse Reactions (6.1, 6.2, 6.3, 6.4, 6.5) in the full prescribing information]*. Localized and systemic infections, including pneumonia, mycobacterial infections, other bacterial infections, invasive fungal infections, such as aspergillosis, candidiasis, or pneumocystis jiroveci pneumonia (PJP) and viral infections including reactivation of hepatitis B virus have occurred in patients taking AFINITOR. Some of these infections have been severe (e.g., leading to sepsis, respiratory or hepatic failure) or fatal. Physicians and patients should be aware of the increased risk of infection with AFINITOR. Complete treatment of pre-existing invasive fungal infections prior to starting treatment with AFINITOR. While taking AFINITOR, be vigilant for signs and symptoms of infection; if a diagnosis of an infection is made, institute appropriate treatment promptly and consider interruption or discontinuation of AFINITOR. If a diagnosis of invasive systemic fungal infection is made, discontinue AFINITOR and treat with appropriate antifungal therapy.

Pneumocystis jiroveci pneumonia, some with a fatal outcome, has been reported in patients who received everolimus. This may be associated with concomitant use of corticosteroids or other immunosuppressive agents. Prophylaxis for PJP should be considered when concomitant use of corticosteroids or other immunosuppressive agents are required.

5.3 Oral Ulceration

Mouth ulcers, stomatitis, and oral mucositis have occurred in patients treated with AFINITOR at an incidence ranging from 44%-78% across the clinical trial experience. Grade 3 or 4 stomatitis was reported in 4%-9% of patients *[see Adverse Reactions (6.1, 6.2, 6.3, 6.4, 6.5) in the full prescribing information]*. In such cases, topical treatments are recommended, but alcohol-, hydrogen peroxide-, iodine-, or thyme- containing mouthwashes should be avoided as they may exacerbate the condition. Antifungal agents should not be used unless fungal infection has been diagnosed *[see Drug Interactions (7.1)]*.

5.4 Renal Failure

Cases of renal failure (including acute renal failure), some with a fatal outcome, have been observed in patients treated with AFINITOR *[see Laboratory Tests and Monitoring (5.7)]*.

5.5 Impaired Wound Healing

Everolimus delays wound healing and increases the occurrence of wound-related complications like wound dehiscence, wound infection, incisional hernia, lymphocele, and seroma. These wound-related complications may require surgical intervention. Exercise caution with the use of AFINITOR in the peri-surgical period.

5.7 Laboratory Tests and Monitoring

Renal Function

Elevations of serum creatinine and proteinuria have been reported in patients taking AFINITOR *[see Adverse Reactions (6.1, 6.2, 6.3, 6.4, 6.5) in the full prescribing information]*. Monitoring of renal function, including measurement of blood urea nitrogen (BUN), urinary protein, or serum creatinine, is recommended prior to the start of AFINITOR therapy and periodically thereafter. Renal function of patients should be monitored particularly where patients have additional risk factors that may further impair renal function.

Blood Glucose and Lipids

Hyperglycemia, hyperlipidemia, and hypertriglyceridemia have been reported in patients taking AFINITOR *[see Adverse Reactions (6.1, 6.2, 6.3, 6.4, 6.5) in the full prescribing information]*. Monitoring of fasting serum glucose and lipid profile is recommended prior to the start of AFINITOR therapy and periodically thereafter as well as management with appropriate medical therapy. More frequent monitoring is recommended when AFINITOR is co-administered with other drugs that may induce hyperglycemia. When possible, optimal glucose and lipid control should be achieved before starting a patient on AFINITOR.

Hematologic Parameters

Decreased hemoglobin, lymphocytes, neutrophils, and platelets have been reported in patients taking AFINITOR *[see Adverse Reactions (6.1, 6.2, 6.3, 6.4, 6.5) in the full prescribing information]*. Monitoring of complete blood count is recommended prior to the start of AFINITOR therapy and periodically thereafter.

5.8 Drug-drug Interactions

Due to significant increases in exposure of everolimus, co-administration with strong CYP3A4/PgP inhibitors should be avoided *[see Dosage and Administration (2.2, 2.5) in the full prescribing information and Drug Interactions (7.1)]*.

A reduction of the AFINITOR dose is recommended when co-administered with a moderate CYP3A4/PgP inhibitor *[see Dosage and Administration (2.2, 2.5) in the full prescribing information and Drug Interactions (7.1)]*.

An increase in the AFINITOR dose is recommended when co-administered with a strong CYP3A4/PgP inducer *[see Dosage and Administration (2.2, 2.5) in the full prescribing information and Drug Interactions (7.2)]*.

5.9 Hepatic Impairment

Exposure to everolimus was increased in patients with hepatic impairment *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

For advanced HR+ BC, advanced PNET, advanced RCC, and renal angiomyolipoma with TSC patients with severe hepatic impairment (Child-Pugh class C), AFINITOR may be used at a reduced dose if the desired benefit outweighs the risk. For patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment, a dose reduction is recommended *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3) in the full prescribing information]*.

For patients with SEGA and mild or moderate hepatic impairment, adjust the dose of AFINITOR Tablets or AFINITOR DISPERZ based on therapeutic drug monitoring. For patients with SEGA and severe hepatic impairment, reduce the starting dose of AFINITOR Tablets or AFINITOR DISPERZ by approximately 50% and adjust subsequent doses based on therapeutic drug monitoring *[see Dosage and Administration (2.4, 2.5) in the full prescribing information]*.

5.10 Vaccinations

During AFINITOR treatment, avoid the use of live vaccines and avoid close contact with individuals who have received live vaccines (e.g., intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines).

For pediatric patients with SEGA that do not require immediate treatment, complete the recommended childhood series of live virus vaccinations according to American Council on Immunization Practices (ACIP) guidelines

prior to the start of therapy. An accelerated vaccination schedule may be appropriate.

5.11 Embryo-fetal Toxicity

Based on the mechanism of action, AFINITOR can cause fetal harm. Everolimus caused embryo-fetal toxicities in animals at maternal exposures that were lower than human exposures. 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 a fetus *[see Use in Specific Populations (8.1)]*.

Advise female patients of reproductive potential to avoid becoming pregnant and to use highly effective contraception while using AFINITOR and for up to 8 weeks after ending treatment *[see Use in Specific Populations (8.6)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in another section of the label *[see Warnings and Precautions (5)]*:

- Non-infectious pneumonitis *[see Warnings and Precautions (5.1)]*.
- Infections *[see Warnings and Precautions (5.2)]*.
- Oral ulceration *[see Warnings and Precautions (5.3)]*.
- Renal failure *[see Warnings and Precautions (5.4)]*.
- Impaired wound healing *[see Warnings and Precautions (5.5)]*.

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

6.3 Clinical Study Experience in Advanced Renal Cell Carcinoma

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

The most common adverse reactions (incidence ≥ 30%) were stomatitis, infections, asthenia, fatigue, cough, and diarrhea. The most common Grade 3-4 adverse reactions (incidence ≥ 3%) were infections, dyspnea, fatigue, stomatitis, dehydration, pneumonitis, abdominal pain, and asthenia. The most common laboratory abnormalities (incidence ≥ 50%) were anemia, hypercholesterolemia, hypertriglyceridemia, hyperglycemia, lymphopenia, and increased creatinine. The most common Grade 3-4 laboratory abnormalities (incidence ≥ 3%) were lymphopenia, hyperglycemia, anemia, hypophosphatemia, and hypercholesterolemia. Deaths due to acute respiratory failure (0.7%), infection (0.7%), and acute renal failure (0.4%) were observed on the AFINITOR arm but none on the placebo arm. The rates of treatment-emergent adverse events (irrespective of causality) resulting in permanent discontinuation were 14% and 3% for the AFINITOR and placebo treatment groups, respectively. The most common adverse reactions (irrespective of causality) leading to treatment discontinuation were pneumonitis and dyspnea. Infections, stomatitis, and pneumonitis were the most common reasons for treatment delay or dose reduction. The most common medical interventions required during AFINITOR treatment were for infections, anemia, and stomatitis.

Table 6 compares the incidence of treatment-emergent adverse reactions reported with an incidence of ≥ 10% for patients receiving AFINITOR 10 mg daily versus placebo. Within each MedDRA system organ class, the adverse reactions are presented in order of decreasing frequency.

Table 6: Adverse Reactions Reported in at Least 10% of Patients with RCC and at a Higher Rate in the AFINITOR Arm than in the Placebo Arm

	AFINITOR 10 mg/day N=274			Placebo N=137		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Any adverse reaction	97	52	13	93	23	5
Gastrointestinal disorders						
Stomatitis[a]	44	4	<1	8	0	0
Diarrhea	30	1	0	7	0	0
Nausea	26	1	0	19	0	0
Vomiting	20	2	0	12	0	0
Infections and infestations[b]	37	7	3	18	1	0
General disorders and administration site conditions						
Asthenia	33	3	<1	23	4	0
Fatigue	31	5	0	27	3	<1
Edema peripheral	25	<1	0	8	<1	0
Pyrexia	20	<1	0	9	0	0
Mucosal inflammation	19	1	0	1	0	0
Respiratory, thoracic and mediastinal disorders						
Cough	30	<1	0	16	0	0
Dyspnea	24	6	1	15	3	0
Epistaxis	18	0	0	0	0	0
Pneumonitis[c]	14	4	0	0	0	0
Skin and subcutaneous tissue disorders						
Rash	29	1	0	7	0	0
Pruritus	14	<1	0	7	0	0
Dry skin	13	<1	0	5	0	0
Metabolism and nutrition disorders						
Anorexia	25	1	0	14	<1	0
Nervous system disorders						
Headache	19	<1	<1	9	<1	0
Dysgeusia	10	0	0	2	0	0
Musculoskeletal and connective tissue disorders						
Pain in extremity	10	1	0	7	0	0
Median duration of treatment (d)		**141**			**60**	

Grading according to CTCAE Version 3.0

[a] Stomatitis (including aphthous stomatitis), and mouth and tongue ulceration.

[b] Includes all preferred terms within the 'infections and infestations' system organ class, the most common being nasopharyngitis (6%), pneumonia (6%), urinary tract infection (5%), bronchitis (4%), and sinusitis (3%), and also including aspergillosis (<1%), candidiasis (<1%), and sepsis (<1%).

[c] Includes pneumonitis, interstitial lung disease, lung infiltration, pulmonary alveolar hemorrhage, pulmonary toxicity, and alveolitis.

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

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

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

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

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

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

Psychiatric disorders: Insomnia (9%)

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

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

Vascular disorders: Hypertension (4%), deep vein thrombosis (< 1%)

Renal and urinary disorders: Renal failure (3%)

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

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

Hematologic disorders: Hemorrhage (3%)

Key laboratory abnormalities are presented in Table 7.

Table 7: Key Laboratory Abnormalities Reported in Patients with RCC at a Higher Rate in the AFINITOR Arm than the Placebo Arm

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

Grading according to CTCAE Version 3.0

[a] Reflects corresponding adverse drug reaction reports of anemia, leukopenia, lymphopenia, neutropenia, and thrombocytopenia (collectively pancytopenia), which occurred at lower frequency.

6.6 Postmarketing Experience

The following adverse reactions have been identified during post approval use of AFINITOR. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate frequency or establish a causal relationship to drug exposure: acute pancreatitis, cholecystitis, cholelithiasis, arterial thrombotic events and reflex sympathetic dystrophy.

7 DRUG INTERACTIONS

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

7.1 Agents That May Increase Everolimus Blood Concentrations

CYP3A4 Inhibitors and PgP Inhibitors

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

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

Concomitant strong inhibitors of CYP3A4/PgP should not be used *[see Dosage and Administration (2.2, 2.5) in the full prescribing information and Warnings and Precautions (5.8)]*.

Use caution when AFINITOR is used in combination with moderate CYP3A4/PgP inhibitors. If alternative treatment cannot be administered reduce the AFINITOR dose *[see Dosage and Administration (2.2, 2.5) in the full prescribing information and Warnings and Precautions (5.8)]*.

7.2 Agents That May Decrease Everolimus Blood Concentrations

CYP3A4/PgP Inducers

In healthy subjects, co-administration of AFINITOR with rifampin, a strong inducer of CYP3A4 and an inducer of PgP, decreased everolimus AUC and C_{max} by 63% and 58% respectively, compared to everolimus treatment alone. Consider a dose increase of AFINITOR when co-administered with strong CYP3A4/PgP inducers if alternative treatment cannot be administered. St. John's Wort may decrease everolimus exposure unpredictably and should be avoided *[see Dosage and Administration (2.2, 2.5) in the full prescribing information]*.

7.3 Drugs That May Have Their Plasma Concentrations Altered by Everolimus

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

A study in healthy subjects demonstrated that co-administration of an oral dose of midazolam (sensitive CYP3A4 substrate) with everolimus resulted in a 25% increase in midazolam C_{max} and a 30% increase in midazolam $AUC_{(0\text{-}inf)}$.

Coadministration of everolimus and exemestane increased exemestane C_{min} by 45% and C_{2h} by 64%. However, the corresponding estradiol levels at steady state (4 weeks) were not different between the 2 treatment arms. No increase in adverse events related to exemestane was observed in patients with hormone receptor-positive, HER2-negative advanced breast cancer receiving the combination.

Coadministration of everolimus and depot octreotide increased octreotide C_{min} by approximately 50%.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D

Risk Summary

Based on the mechanism of action, AFINITOR can cause fetal harm when administered to a pregnant woman. Everolimus caused embryo-fetal toxicities in animals at maternal exposures that were lower than human exposures. If this drug is used during pregnancy or if the patient becomes pregnant while taking the drug, apprise the patient of the potential hazard to the fetus *[see Warnings and Precautions (5.11)]*.

Animal Data

In animal reproductive studies, oral administration of everolimus to female rats before mating and through organogenesis induced embryo-fetal toxicities, including increased resorption, pre-implantation and post-implantation loss, decreased numbers of live fetuses, malformation (e.g., sternal cleft), and retarded skeletal development. These effects occurred in the absence of maternal toxicities. Embryo-fetal toxicities in rats occurred at doses ≥ 0.1 mg/kg (0.6 mg/m^2) with resulting exposures of approximately 4% of the exposure ($AUC_{0\text{-}24h}$) achieved in patients receiving the 10 mg daily dose of everolimus. In rabbits, embryotoxicity evident as an increase in resorptions occurred at an oral dose of 0.8 mg/kg (9.6 mg/m^2), approximately 1.6 times either the 10 mg daily dose or the median dose administered to SEGA patients on a body surface area basis. The effect in rabbits occurred in the presence of maternal toxicities.

In a pre- and post-natal development study in rats, animals were dosed from implantation through lactation. At the dose of 0.1 mg/kg (0.6 mg/m^2), there were no adverse effects on delivery and lactation or signs of maternal toxicity; however, there were reductions in body weight (up to 9% reduction from the control) and in survival of offspring (~5% died or missing). There were no drug-related effects on the developmental parameters (morphological development, motor activity, learning, or fertility assessment) in the offspring.

8.3 Nursing Mothers

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

8.5 Geriatric Use

In the randomized advanced hormone receptor positive, HER2-negative breast cancer study, 40% of AFINITOR-treated patients were ≥ 65 years of age, while 15% were 75 years and over. No overall differences in effectiveness were observed between elderly and younger patients. The incidence of deaths due to any cause within 28 days of the last AFINITOR dose was 6% in patients ≥ 65 years of age compared to 2% in patients < 65 years of age. Adverse reactions leading to permanent treatment discontinuation occurred in 33% of patients ≥ 65 years of age compared to 17% in patients < 65 years of age *[see Warnings and Precautions (5.6) in the full prescribing information]*.

In two other randomized trials (advanced renal cell carcinoma and advanced neuroendocrine tumors of pancreatic origin), no overall differences in safety or effectiveness were observed between elderly and younger patients. In the randomized advanced RCC study, 41% of AFINITOR treated patients

were ≥ 65 years of age, while 7% were 75 years and over. In the randomized advanced PNET study, 30% of AFINITOR-treated patients were ≥ 65 years of age, while 7% were 75 years and over.

Other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

No dosage adjustment in initial dosing is required in elderly patients, but close monitoring and appropriate dose adjustments for adverse reactions is recommended *[see Dosage and Administration (2.2), Clinical Pharmacology (12.3) in the full prescribing information]*.

8.6 Females and Males of Reproductive Potential

Contraception

Females

AFINITOR can cause fetal harm when administered to a pregnant woman. Advise female patients of reproductive potential to use highly effective contraception while receiving AFINITOR and for up to 8 weeks after ending treatment *[see Use in Specific Populations (8.1)]*.

Infertility

Females

Menstrual irregularities, secondary amenorrhea, and increases in luteinizing hormone (LH) and follicle stimulating hormone (FSH) occurred in female patients taking AFINITOR. Based on these clinical findings and findings in animals, female fertility may be compromised by treatment with AFINITOR *[see Adverse Reactions (6.2, 6.4, 6.5) and Nonclinical Toxicology (13.1) in the full prescribing information]*.

Males

AFINITOR treatment may impair fertility in male patients based on animal findings *[see Nonclinical Toxicology (13.1) in the full prescribing information]*.

8.7 Renal Impairment

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

8.8 Hepatic Impairment

The safety, tolerability and pharmacokinetics of AFINITOR were evaluated in a 34 subject single oral dose study of everolimus in subjects with impaired hepatic function relative to subjects with normal hepatic function. Exposure was increased in patients with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

For advanced HR+ BC, advanced PNET, advanced RCC, and renal angiomyolipoma with TSC patients with severe hepatic impairment, AFINITOR may be used at a reduced dose if the desired benefit outweighs the risk. For patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment, a dose reduction is recommended *[see Dosage and Administration (2.2) in the full prescribing information]*.

For patients with SEGA who have severe hepatic impairment (Child-Pugh class C), reduce the starting dose of AFINITOR Tablets or AFINITOR DISPERZ by approximately 50%. For patients with SEGA who have mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment, adjustment to the starting dose may not be needed. Subsequent dosing should be based on therapeutic drug monitoring *[see Dosage and Administration (2.4, 2.5) in the full prescribing information]*.

10 OVERDOSAGE

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

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

Manufactured by:
Novartis Pharma Stein AG
Stein, Switzerland

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

T2014-66
July 2014

About the Cover
The branches in this schematic represent the genomic architecture and evolution of clear cell renal cell carcinomas (RCC) as developed by a European consortium. They are what the consortium calls the "phylogenetic trees for RCC." (Courtesy of the PREDICT Consortium).

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KCJ GUEST EDITOR'S MEMO

Revealing More of the Biology of Kidney Cancer, and Ultimately, Its Targets


Janice P. Dutcher, MD

The genomic architecture and evolution of clear cell renal cell carcinomas (RCC) depicted on the cover of this issue represent more than just branches of what a consortium calls "phylogenetic trees for RCC." These spoke-like directions might be a metaphor for investigations into the biology of the disease itself, branching out into myriad avenues as we seek to define and redefine biomarkers and gain more of a foothold on the heterogeneity of the gene sequence in RCC.

We have known for many years that the most common histological subtype, clear cell RCC, is associated with abnormalities in the Von Hippel-Lindau tumor suppressor gene (*VHL*) in almost all cases. Drugs able to inhibit the vascular endothelial growth factor (VEGF) pathway such as bevacizumab, sunitinib, pazopanib and axitinib are active in clear cell RCC. However, no drugs have been developed to date able to target the loss of tumor suppressor genes, as is the case of *VHL* in RCC, and VEGF inhibitors do not directly target tumor cells but the tumor microenvironment. No predictive biomarkers in clear cell RCC have been identified yet and around 30% of patients will not benefit from treatment.

This is why the work of the PREDICT Consortium, as reviewed by investigators in this issue of the *Kidney Cancer Journal* should be of interest to all caregivers hoping for additional clues to identifying predictive biomarkers. Unlike the therapeutic arena, where breakthroughs or at least milestones in targeted therapies occasionally appear, the progress in defining biomarkers is glacial and we only obtain advances in small increments as investigations proceed over the years. Yet, much like peeling away the layers of an onion, more of the intratumor heterogeneity of renal tumors is being revealed. The goal of course would be to devise a pre-treatment test able to predict with some reliability the efficacy of cytokines, VEGF therapies and mammalian target of rapamycin (mTOR) inhibitors. The challenge of doing so remains daunting because the responsiveness to treatment can differ significantly between patients even when their tumors have been classified within the same histological subtype, grade and/or stage.

Much progress has been made, for example, in identifying predictive markers for the use of high-dose interleukin-2 (IL-2). Efforts in this area have led to much improved identification of patients more likely to re-

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Kidney Cancer Journal Author Guidelines

Scope of Manuscripts

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

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

Manuscript Submission

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

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Peer Review and Editing

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

Conflict of Interest

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

Manuscript Preparation

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

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

References

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

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Essential Peer-Reviewed Reading in Kidney Cancer

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

Characterizing the impact of lymph node metastases on the survival outcome for metastatic renal cell carcinoma patients treated with targeted therapies. Kroeger N, Pantuck AJ, Wells JC, et al. *Eur Urol*. 2014 Dec 15. pii: S0302-2838(14)01249-4. doi: 10.1016/j.eururo.2014.11.054. [Epub ahead of print]

Summary: This study evaluated the clinicopathological features, survival outcome, and treatment response in mRCC patients with lymph node metastases (LNM) vs those without LNM after treatment with targeted therapies (TT). Patients (N=2996) were first analyzed without consideration of lymph node (LN) localization or histologic subtype. Additional analyses (N=1536) were performed in subgroups of patients with supradiaphragmatic (SPD) LNM, subdiaphragmatic (SBD) LNM, and patients with LNM in both locations (SPD+/SBD+) without histologic considerations, and then separately in clear cell RCC (ccRCC) and non-clear cell RCC (nccRCC) patients, respectively. The primary outcome was overall survival (OS) and the secondary outcome was progression-free survival (PFS). All patients with LNM had worse PFS (P=0.001) and OS (P<0.001) compared to those without LNM. Compared to patients without LNM (PFS 8.8 mo; OS 25.1 mo), any SBD LNM involvement was associated with worse PFS (SBD, 6.8 mo; P=0.003; SPD+/SBD+, 5.5 mo; P<0.001) and OS (SBD, 16.2 mo; P<0.001; SPD+/SBD+, 11.5 mo; P<0.001). Both SBD and SPD+/SBD+ LNM were retained as independent prognostic factors in multivariate analyses (MVA) for PFS (P=0.006 and P=0.022, respectively) and OS (both P<0.001), while SPD LNM was not an independent risk factor. Likewise, in ccRCC, SBD LNM (19.8 mo) and SPD+/SBD+ LNM (12.85 mo) patients had the worst OS. SPD+/SBD+ LNM (P=0.006) and SBD LNM (P=0.028) were independent prognostic factors for OS in MVA, while SPD LNM was not significant (P=0.301). The study is limited by its retrospective design and the lack of pathologic evaluation of LNM in all cases.

Conclusion: The metastatic spread of RCC to SBD lymph nodes is associated with poor prognosis in mRCC patients treated with TT. The presence of lymph node metastases below the diaphragm is associated with shorter survival outcome when metastatic renal cell carcinoma (mRCC) patients are treated with targeted therapies. Clinical trials should evaluate whether surgical removal of regional lymph nodes at the time of nephrectomy may improve outcomes in high-risk RCC patients.

Long-term survival rates after resection for locally advanced kidney cancer: Memorial Sloan Kettering Cancer Center 1989-2012 experience. Bazzi WM, Sjoberg DD, Feuerstein MA, et al. *J Urol*. 2014 Dec 15. pii: S0022-5347(14)05073-3. doi: 10.1016/j.juro.2014.12.022. [Epub ahead of print]

Summary: The purpose of this study was to analyze the Memorial Sloan Kettering Cancer Center 23-year experience with surgical resection and utilization of concurrent adrenalectomy and lymphadenectomy for locally advanced non-metastatic renal cell carcinoma(RCC). The data are based on a retrospective review of 802 patients who underwent nephrectomy, with or without concurrent adrenalectomy or lymphadenectomy, for locally advanced RCC defined as stage ≥T3 and M0. Patients who had undergone adjuvant treatment within 3 months of surgery, had <3 months of follow-up, or had bilateral renal masses at presentation were excluded. Five- and 10-year progression-free and overall survivals were estimated using the Kaplan-Meier method. Differences between groups were analyzed by the log-rank test. A total of 596 (74%) and 206 (26%) patients underwent radical and partial nephrectomy, respectively. RCC progressed in 189 patients and 104 died from it. Median follow-up for patients who did not progress was 4.6 years. Symptoms at presentation, American Society of Anesthesiologists classification, tumor stage, histologic subtype, grade, and lymph node status were significantly associated with progression-free and overall survival. On multivariate analysis, adrenalectomy utilization decreased over time with odds ratio .82/year, whereas lymphadenectomy increased with odds ratio 1.16/year. Larger tumors were associated with a higher likelihood of concurrent adrenalectomy and lymphadenectomy.

Conclusion: In this series of patients with locally advanced non-metastatic RCC, those who were in good health, asymptomatic upon presentation, had T3 tumors, and negative lymph nodes had favorable survival. Further, there has been a trend toward more selective use of adrenalectomy and increased use of lymphadenectomy.

Activation of aryl hydrocarbon receptor promotes invasion of clear cell renal cell carcinoma and is associated with poor prognosis and cigarette smoke. Ishida M, Mikami S, Shinojima T, et al. *Int J Cancer*. 2014 Dec 19. doi: 10.1002/ijc.29398. [Epub ahead of print]

Summary: Although exposure to environmental pollutants is one of the risk factors for renal cell carcinoma (RCC), its relationship with carcinogenesis and progression of RCC remains unknown. This study elucidated the role of the aryl hydrocarbon receptor (AhR), a major mediator of carcinogenesis caused by environmental pollutants, in RCC progression. Expression of AhR was investigated in 120 RCC patients using immunohistochemistry, and its relationship with clinicopathological parameters and prognoses was statistically analyzed. RCC cell lines were exposed to indirubin or 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), AhR ligands, to activate the AhR pathway, or were transfected with small interfering RNA (siRNA) for AhR. The expression of the AhR target genes CYP1A1 and CYP1B1, matrix metalloproteinases (MMPs), and invasion through Matrigel™ were then examined. AhR was predominantly expressed in the nuclei of high-grade clear cell

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

High-dose Interleukin-2 Effective in mRCC Pre-treated With VEGF-targeted Therapies

LUGANO/GENEVA, SWITZERLAND—High-dose interleukin-2 (HD-IL2) can be effective in selected metastatic renal cell cancer patients pre-treated with VEGF-targeted agents, according to research presented at the 2014 ESMO Symposium on Immuno-Oncology in Geneva, Switzerland.

Lead author Dr Manon Evans, research fellow at the Christie Hospital in Manchester, UK, reported: "We have previously demonstrated that pre-selecting patients by a combination of clinical and histological criteria can generate impressive results in the treatment-naïve population." Patients were classified as 'Favorable' or 'Other' based on their histological makeup.

The current study is a retrospective analysis of 180 patients treated with HD-IL2 at the Christie NHS Foundation Trust over the past 10 years. The majority were treated in the first-line setting, with a smaller cohort receiving treatment following VEGF-targeted agents. The researchers also investigated whether expression of the biomarker carbonic anhydrase IX (CAIX) correlated with outcome and could potentially be added to the selection criteria for HD-IL2 therapy. A total of 180 patients with mRCC were treated with HD-IL2, 145 in the treatment-naïve cohort and 35 in the pre-treated cohort. Of these, a total of 158 had 'Favorable' histology of whom over 45% responded with a 23% complete remission rate. Of those achieving a complete response to therapy, over 75% are alive and disease free. The median overall survival in those achieving a complete response has not yet been reached. There was no significant difference in response or survival rate between the two treatment cohorts.

CAIX positivity correlated favorably with response and survival as did disease burden and tolerance of treatment. All patients experienced toxicity as anticipated. The incidence of treatment-related myocarditis was higher in the pre-treated cohort (8.5%) compared to the treatment-naïve group (3.4%). Dr Evans added: "Our data confirms that there remains a role for HD-IL2 in the management of mRCC and demonstrates, in a selected population, complete responses of over 20%, most of which are durable. In contrast to initial reports, it can be safe and effective in carefully selected patients pre-treated with VEGF-targeted agents with response rates and complete responses similar to first-line therapy. Its application should strongly be considered in both the treatment-naïve and pre-treated population."

She continued: "Outcomes were clearly superior in patients with 'Favourable' histology (incorporating those with solid/alveolar clear cell RCC) but there were rare durable complete remissions in patients with 'Other' histologies and the role of HD-IL2 in this group is less well defined with further assessment required."

Kidney Cancer Cases Show Sharp Rise in UK

LONDON—-The number of cases of kidney cancer diagnosed each year in Great Britain has risen over 9,000 for the first time, new figures from Cancer Research UK show today. Experts believe that obesity could be one of the key factors behind the staggering 135 per cent rise in kidney cancer rates over the last 35 years.

FDA Approves Nivolumab, a PD-1 Inhibitor

BETHESDA, MD—-The FDA has granted accelerated approval to Opdivo (nivolumab), a new treatment for patients with unresectable or metastatic melanoma who no longer respond to other drugs. Nivolumab is still being evaluated in renal cell carcinoma and is the second PD-1 inhibitor to be approved by the FDA for melanoma. The agent is effective by inhibiting the PD-1 protein on cells, which blocks the body's immune system from attacking melanoma tumors. Results with nivolumab from a phase 2 study were reported at the 2014 meeting of the American Society of Clinical Oncology.

Combination of Bevacizumab and Erlotinib Effective in Advanced Papillary RCC

BARCELONA, SPAIN—-The combination of bevacizumab and erlotinib produced excellent response rates with tolerable side effects in patients with advanced papillary renal cell carcinoma (pRCC) and in patients with a highly aggressive form of pRCC called hereditary leiomyomatosis and renal cell cancer (HLRCC). Results were presented by Dr Ramaprasad Srinivasan, head of the Molecular Cancer Therapeutics Section, Urologic Oncology Branch, of the National Cancer Institute, who reported at the 26th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics in Barcelona.

He told the symposium attendees: "The genetic and biochemical events that lead to papillary renal cell carcinoma are different to those that lead to the more common form of kidney cancer, clear cell renal carcinoma. Treatments that are effective in clear cell RCC are not particularly effective in pRCC. Some forms of pRCC, particularly those associated with HLRCC, are characterized by altered cellular metabolism; the tumor cells obtain energy from a process called aerobic glycolysis, and they require high levels of glucose to survive. We believe the combination of erlotinib and bevacizumab may target this particular weakness, at least partly, by impairing glucose delivery to the tumor cells."

Dr Srinivasan and researchers at the NCI Urologic Oncology Branch recruited 41 patients to a phase II clinical trial of bevacizumab combined with erlotinib. The treatment was continued until the disease progressed or there were unacceptable toxic side effects. Twenty patients in the first group had advanced HLRCC and 21 patients in the second

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Emerging Data from the PREDICT Consortium: Identifying and Validating Biomarkers in RCC From a New Initiative

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Established in 2010, a multi-national consortium is investigating predictive biomarkers in renal cell carcinoma (RCC) to achieve better clinical outcomes through personalized treatment. Addressing a broad range of issues, including tumor heterogeneity and phenotypic factors involved in resistance to treatment, the consortium has proposed novel strategies and new methods to understand the biological complexity of RCC. This report is one of the first papers to chronicle its efforts and analyze its implications.

Background

Renal cell carcinoma (RCC) is the most frequent kidney cancer and accounts for approximately 3% of all adult malignancies.[1] It is estimated that around 60,000 new cases are diagnosed in both the European Union (EU) and the United States (US) every year and its incidence is increasing.[2,3] A large number of drugs have been approved in this malignancy in recent years.[4] In spite of this array of new treatment options, the cure of patients affected by advanced RCC is rare and the development of tumor resistance occurs in virtually all cases.[5]

The heterogeneity of RCC might be responsible in part for this lack of curative therapies. The most common RCC histological subtype, clear cell RCC, is found in approximately 75% of cases.[6] Other histologies such as type I or II papillary, chromophobe or translocation-associated RCCs are less frequent.[7] Each of these sub-types has different clinical behaviour and sensitivity to targeted agents, which reflects their different biology and pathogenesis. However, responsiveness to treatment can differ significantly between patients even when their tumors have been classified within the same histological subtype, grade and/or stage.[7] In addition, no predictive biomarkers have been identified to date. Thus, unlike other tumor types such as melanoma,[8,9] non-small-cell lung cancer (NSCLC)[10] or gastrointestinal stromal tumors (GIST)[11] in which treatment efficacy is based on targeting a specific driver mutation that results in an activating kinase, molecular profiling has no role in RCC treatment. Cytokines, vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) inhibitors are used in routine clinical practice in advanced RCC without pre-treatment screening tests able to predict their efficacy. Also, increasing evidence strongly suggest in recent years that intra-tumor heterogeneity (ITH) is another relevant factor in RCC treatment outcomes.[12]

Therefore, there is an urgent need in defining reliable and validated predictive biomarkers of response to the existing drugs and to identify novel potential targets. For this purpose, the EU multi-disciplinary personalised RNA interference to enhance the delivery of individualised cytotoxic and targeted therapeutics (PREDICT) consortium was created in 2010. This multi-national consortium was established in order to investigate predictive biomarkers in RCC to achieve better clinical outcomes through personalized treatment.[13]

Keywords: Renal cell carcinoma, predictive biomarkers, PREDICT Consortium, somatic mutations, histology, *VHL*, tumor heterogeneity.

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In this article, the background for the search for predictive biomarkers in RCC by the PREDICT consortium will be analyzed as well as the current available results and future perspectives.

PREDICT Background

Inter-tumor Heterogeneity. As mentioned earlier, RCC is a heterogeneous group of diseases with different characteristics that share the common feature of arising in the renal parenchyma. There are many histological classifications of RCC but even within the same tumor subtype, clinical outcomes can be very different. Several prognostic models based on clinical characteristics have been proposed in an attempt to better define the management of patients affected by advanced RCC. The two most widely used models, the one proposed by Motzer et al[14] and the one proposed by Heng et al,[15] do not take into account the histological subtype when categorizing patients into risk groups. Interestingly, both models do not differ significantly in spite of being elaborated respectively before and during the era of targeted therapies.

The most common histological subtype, clear cell RCC, is associated with abnormalities in the Von Hippel-Lindau tumor suppressor gene (*VHL*) in almost all cases.[16] Drugs able to inhibit the VEGF pathway such as bevacizumab, sunitinib, pazopanib and axitinib are active in clear cell RCC.[4] However, no drugs have been developed to date able to target the loss of tumor suppressor genes, as is the case of *VHL* in RCC, and VEGF inhibitors do not directly target tumor cells but the tumour micro-environment. Similarly to other tumor types in which anti-VEGF therapy has proved to be effective such as colorectal cancer,[17-20] NSCLC (21), cervical cancer[22] and ovarian cancer,[23,24] no predictive biomarkers in clear cell RCC have been identified yet and around 30% of patients will not benefit from treatment. Other less frequent RCC histologies such as papillary or chromophobe have also been associated with different mutations[25,26] but no biomarkers for response to treatment have been found either.

Intra-tumor Heterogeneity. A growing body of evidence published in recent years suggests that genetic ITH plays a key role in the response and resistance of RCC to treatment. Initial observations of RCC patients with radiologic response to treatment in some lesions and absence of response or progression in other lesions triggered the hypothesis that not all metastatic deposits from a same primary tumor share the same biologic characteristics.

The importance of ITH was first reported nearly 30 years ago when Ljungberg et al analysed 196 tissue samples from 25 RCCs and found differences in DNA ploidy within the same tumor.[27] The same group reported nearly ten years later the results of a study conducted in 200 consecutive RCCs in which DNA ploidy patterns were analyzed in multiple samples from each tumor using flow cytometry and compared with clinical outcome. Heterogeneity was reported in 56% of tumours and aneuploid and diploid cell clones were seen in 79% of heterogeneous tumors. Homogeneously diploid tumors were found to have a lower incidence of local tumor spread compared with tumors with aneuploid cell clones ($P \leq 0.001$). In addition, the presence of aneuploidy in at least one sample was reported as a significant adverse prognostic factor ($P < 0.001$). The authors suggested that multiple tumor samples should be investigated in RCC given the high frequency of heterogeneity.[28] On the other hand, Ruiz-Cerdá et al found lower rate of ITH (22%) and they were not able to demonstrate its relationship with the biological behaviour of the tumor.[29] Furthermore, comparative genomic hybridization analysis was performed in 32 clear cell RCC metastases in another study and it was found that in 6 cases (32%) they were genetically almost completely different from the primary tumor.[30]

The heterogeneity of the VHL gene sequence in RCC has also been evaluated. Fifty-three clear cell and papillary RCC samples were assessed by fluorescence in situ hybridization (FISH) for *VHL* and results were correlated with predictive factors for RCC progression such as histopathological phenotype or proliferative activity. *VHL* deletion was detected in 69% of clear cell RCCs but in no cases of papillary. Interestingly, these *VHL* deletions were highly heterogeneous within individual tumors. Moreover, cell populations with and without *VHL* deletions were also seen in the same tumor, indicating that in some cases clear cell RCCs may develop independently of *VHL* aberrations.[31] Further investigation showed that *VHL* mutational status can differ between primary RCC and metastasis. Sequencing of VHL gene in paired primary and metastases samples from 10 patients showed genotype inconsistency in 40% of cases. However, when *VHL* was mutated in both samples it was found that the mutation was the same.[32]

Results of the PREDICT Consortium

The original goal of the PREDICT consortium was to identify and validate genomic or transcriptomic predictive biomarkers of drug response in RCC analysing pre-operative tissue derived from clinical trials using established and novel methods to integrate comprehensive tumor-derived genomic data with personalized tumor-derived small hairpin RNA and high-throughput small interfering RNA screens.[13] An initial question was the extent to which a biopsy from a large primary kidney tumor was representative of the molecular landscape of the primary tumor or indeed metastatic sites. Our first efforts therefore addressed this issue.

The first published results derived from the evaluation of tumor samples from 4 consecutive patients with metastatic RCC enrolled in the E-PREDICT trial (EudraCT number 2009-013381-54). Tumor tissue was obtained from biopsy performed before 6 weeks of treatment with the mTOR inhibitor everolimus and from nephrectomy performed after a 1-week washout period **(Figure 1).** Whole-exome multiregion spatial sequencing on DNA extracted from fresh frozen samples obtained from two patients and single-nucleotide polymorphism (SNP) array

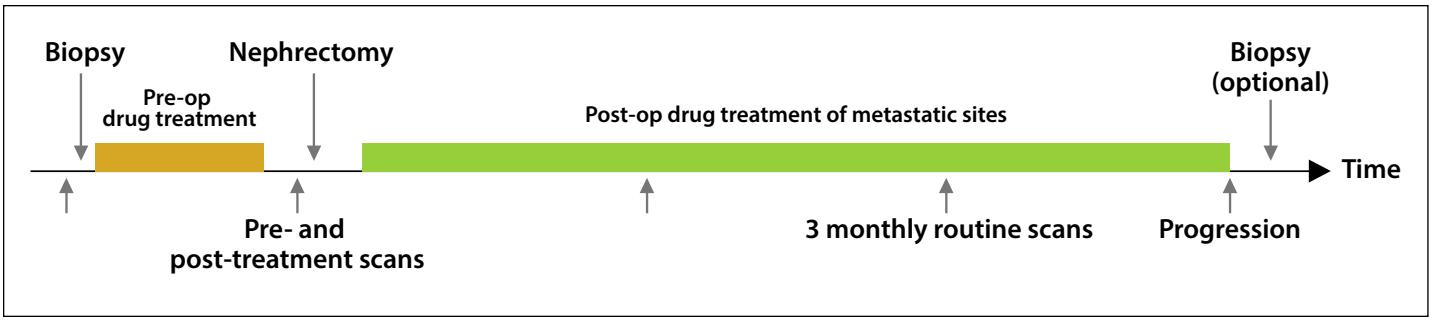

Figure 1. PREDICT strategy for tumor samples. Extracted from Swanton C et al. Predictive biomarker discovery through the parallel integration of clinical trial and functional genomics datasets. *Genome Med*. 2010;2(8):53.

analysis were performed.

Results showed that 63-69% of all somatic mutations observed in multiple biopsies of two primary tumors and their associated metastases were not detectable ubiquitously across all biopsies, which suggests limited power of a unique biopsy to identify the whole range of mutations present within a tumor. Also, mutational ITH for a number of tumor-suppressor genes was seen. However, these mutations converged on loss of function. For instance, multiple distinct and spatially separated inactivating mutations in *SETD2, PTEN,* and *KDM5C* were observed, indicating parallel evolution with the presence of recurrent targets subject to loss of function mutations. Moreover, good and poor prognosis gene-expression signatures were observed in different regions within the same tumor and 26 out of 30 tumor samples harboured divergent allelic-imbalance profiles with ploidy heterogeneity being found in two of four tumors. In addition, mutational landscapes of two metastases were found to be more similar to each other than to the primary tumour in one patient.[33,34]

We have recently extended these observations in a larger (although still small) number of tumors. Exome sequencing of multiple regions (M-seq) was performed in 10 stage T2–T4 primary clear cell RCCs and in a subset of associated metastases. ITH was observed in all cases: 67% of coding somatic mutations, 73% of driver mutations in known cancer genes and 75% of driver copy number changes were not identified in every analysed region per tumor, which can lead to incorrect estimates of the prevalence of driver mutations if a single biopsy is performed **(Table).** Furthermore, subclones were found to be spatially separated within the same tumor. However, several somatic mutations and DNA copy number aberrations were detected across all analysed regions in each tumor, indicating their monoclonal origin. ITH increased with the number of samples analysed and only chromosome 3p loss and *VHL* mutations were found to be ubiquitous events.[35]

A rational therapeutic strategy is to target these 'truncal drivers'. However, results with this approach are difficult to achieve since these founders events result in inactivation of tumor suppressor genes and this is not directly targetable. On the other hand, targeting mutations that appear temporally and spatially distant from the critical truncal events shared by every clear cell RCC (branch mutations) is expected to have less activity. Clinical efficacy of mTOR inhibitors might represent a good example of this. In recent years, 6 randomised clinical trials with the mTOR inhibitors everolimus and temsirolimus have been reported.[36-41] Only in two of them the outcomes were more favourable in the mTOR inhibitor than the control arm.[36,37] Indeed, a trial that compared temsirolimus with sorafenib in patients that had progressed on sunitinib showed worse overall survival (OS) with mTOR inhibition.[39]

Table. Prevalence of mutations observed in various tumor-suppressor genes.

	Prevalence in TCGA samples (N=102 samples)	Prevalence in all M-seq samples (N=79 samples)	Prevalence in cases based on M-seq (N=10 cases)	Prevalence cases/prevalence M-seq samples
PBRM1	42%	39%	60%	1.5
SETD2	18%	27%	30%	1,1
BAP1	21%	23%	40%	1.7
KDM5C	7%	11%	10%	0.9
TP53	5%	6%	40%	6.7
ATM	3%	4%	10%	2.5
ARID1A	6%	1%	10%	10.0
PTEN	5%	10%	20%	2.0
mTOR	9%	8%	10%	1.3
PIK3CA	3%	4%	20%	5.0
TSC2	2%	6%	10%	1.7
PI3K-mTOR	18%	28%	60%	2.1

Since alterations in the mTOR pathway are not infrequent in RCC, these results are not easy to understand. However, mTOR mutations, although frequent, are not 'truncal' but 'branch' events.[33,35] This could explain why mTOR inhibitors are generally less effective in unselected patients than VEGF inhibitors, which target alterations (upregulation of VEGF and PDGF expression) derived by loss-of-function truncal events (inactivation of *VHL*) **(Figure 2).**

The PREDICT consortium has also demonstrated that other alterations beyond VHL in up to 36 driver muta-

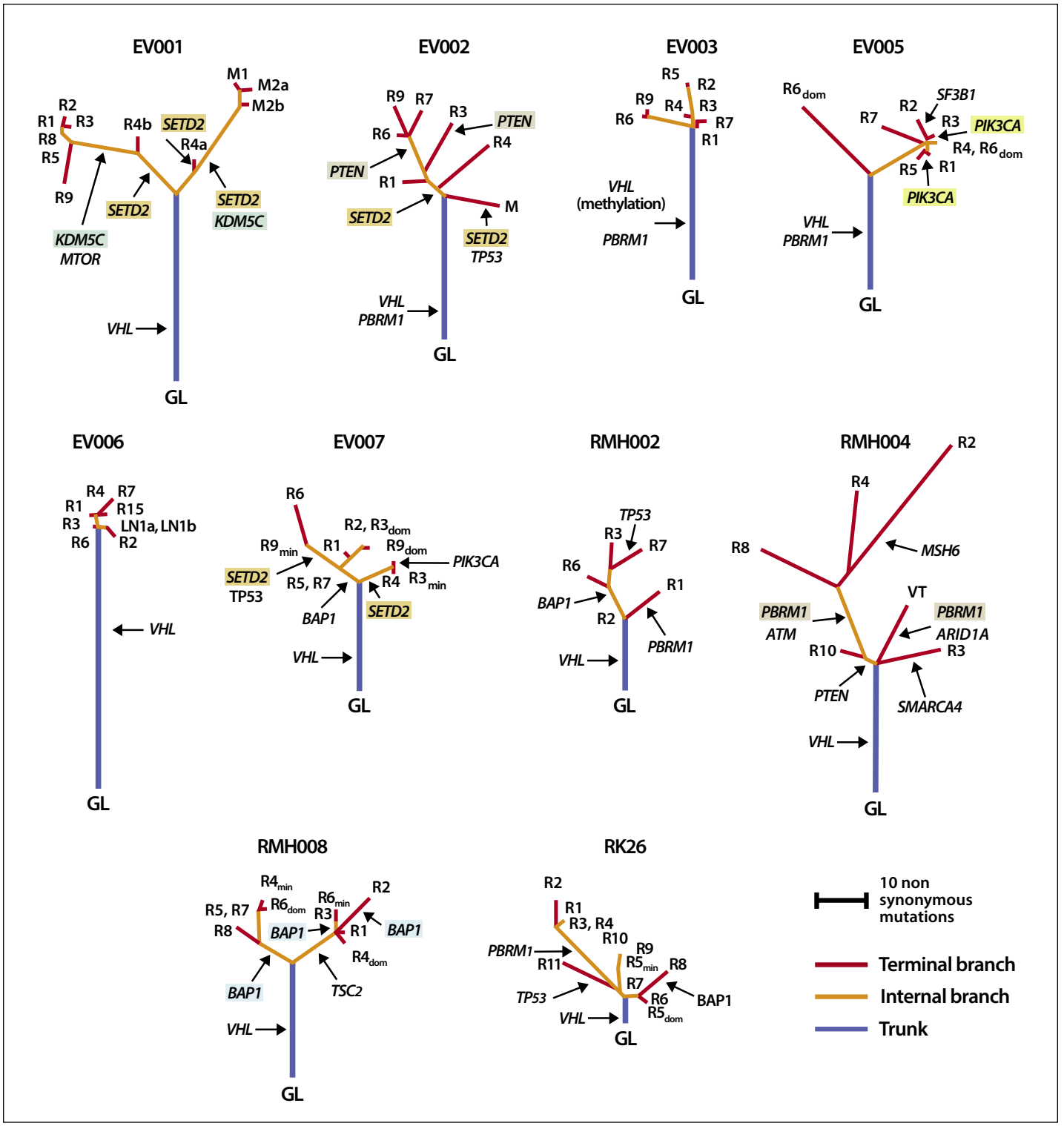

Figure 2. Phylogenetic trees for ten clear cell RCCs proposed by PREDICT. Extracted from Gerlinger M et al. Genomic architecture and evolution of clear cell renal cell carcinomas defined by multiregion sequencing. *Nat Genet*. 2014;46(3):225-33.

tions occur spatially separated and at a later stage in the evolution of clear cell RCC. Some of these mutations are located in PBRM1, SETD2, KDM5C, PTEN, PIK3CA, BAP1, ARID1A and SMARCA4 genes. This variety of temporally and spatially separated mutations suggests that the different clinical outcomes of patients affected by clear cell RCC might be determined by new abnormalities acquired by the tumor along its evolution. Therapeutic intervention might select tumor subclones driven by these new mutations which might confer resistance to treatment[35] **(Figure 2)**.

In order to identify those potentially low-frequency subclones, multiple biopsies, in collaboration with sequencing, laboratory and informatics expertise, are essen-

tial. The Tracking Renal Cancer Evolution Through Treatment (Rx) (TRACERx Renal Cancer) study is currently pursuing this approach. This study aims to recruit 300 patients with renal cancer from the United Kingdom over 5 years and will collect tissue samples of the primary tumor at surgery and subsequently if the disease recurs, alongside blood samples and clinicopathological data.

Future View

Initial data from PREDICT studies have shown that a deeper understanding of ITH is an essential first step in the finding of predictive biomarkers in RCC.[33,35] Recently published results suggest that ITH is also crucial in other types of cancer. Thus, similarly to RCC, branched evolution has also recently been described in NSCLC, with driver mutations found before and after subclonal diversification which can directly affect treatment efficacy.[42] Furthermore, ITH analysis in a specific sub-type of localized NSCLC (lung adenocarcinoma) showed that patients who relapsed had significantly larger fractions of subclonal mutations in their primary tumors than patients without relapse.[43]

In addition, emerging data in another tumor, malignant melanoma, further support the relevance of ITH in response and resistance to treatment. It has been recently described that, whereas resistance to BRAF inhibitors in BRAF V600 mutant melanoma is caused by reactivation of the mitogen-activated protein kinase (MAPK) pathway in the majority of cases or less frequently by PI3K-PTEN-AKT-upregulating alterations, distinct molecular abnormalities in both resistance pathways are concurrently present in the same tumor or among multiple tumors from the same patient.[44] Therefore, convergent phenotypic and branched evolution seems to play an important role in resistance to treatment in melanoma as well.

Conclusion

It is necessary to find predictive biomarkers that help to optimize personalized treatment for patients affected by RCC. Novel strategies such as the ones proposed by the multi-national PREDICT consortium are therefore needed. These new methods have already helped to understand the complexity of the biology of this tumour and its evolution through space and time. A series of studies that will provide further information are ongoing.

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'Expert Dialogues' Meeting Brings Together RCC Opinion Leaders to Review Progress, Envision Future Breakthroughs

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London served as the site for the thought-provoking 2014 Expert Dialogues meeting, an annual event that brings together renal cell carcinoma (RCC) experts and clinician delegates from around the world to examine previous progress, explore recent data, and plan future collaborations in the world of metastatic RCC.

The meeting was hosted by Professor Bernard Escudier from the Institut Gustave Roussy, Paris, and it began with a keynote from David Gilham of the University of Manchester who reviewed current potential for novel immunotherapies in the treatment of metastatic RCC. While many researchers and clinicians are awaiting the expected approval of PD-1 and/or PD-L1 immunotherapies for metastatic RCC, Gilham specifically focused on the potential of using chimeric antigen receptor (CAR) T-cell therapies. This approach uses retroviruses to extracorporally introduce genes encoding chimeric receptors into a patient's own T-cells and then expanding those cells before reinfusing them into the patient. The technology requires patients to receive non-ablative conditioning therapy with drugs like cyclophosphamide or fludarabine shortly before re-infusion in order to "make room" for the engineered cells. After, the infusion high-dose IL-2 further stimulates CAR T-cell expansion *in vivo*. While CAR therapy has shown impressive potential in hematologic malignancies, there is still much work to be done in solid tumors, including RCC.[1]

QOL as a Trials Endpoint

In a much different plenary presentation, Jennifer Beaumont of Northwestern spoke about using quality of life as a clinical trials end-point. She explained that traditional efficacy and safety end-points don't measure a patient's symptom burdens. FDA guidance now strongly encourages the use of patient-focused end-points, including data directly obtained from patients. Beaumont cited the FDA's recent rejection of Provectus Pharmaceuticals' request for breakthrough status for PV-10 (rose Bengal disodium in 0.9% saline) for use against locally advanced cutaneous melanoma as an example of the agencies' drive to incorporate these measures. In its rejection letter, the FDA noted that there was "insufficient information provided in the package of data from Pro-vectus to ascertain improvement in or relief of tumor-related symptoms on pain, bleeding, or tumor ulcera- tion." Beaumont suggested that future RCC trials should at least include validated instruments such as the FACT–Kidney Symptom Index–Disease-Related Symptoms subscale (FKSI-DRS), the Renal Cell Carcinoma-Symptom Index (RCC-SI), or the Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI). She went on to detail the Quality-adjusted Time Without Symptoms of disease and Toxicity (Q-TWiST) model, which essentially combines both quality of life and survival end-points into one outcomes measurement.

Addressing the Need for 'Real World' Data in RCC

Marc Matrana of the Ochsner Cancer Institute in New Orleans and Norbert Marschner, CEO of iOMEDICO in Germany spoke about using real-world data to supplement and complement clinical trial data (**Figures 1,2**). The speakers noted that while over a million patients have metastatic RCC world-wide our current treatment algorithms have been largely based on the outcomes of approximately 2,400 highly selected patients who have been treated on pivotal trials with approved first-line

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Figure 1. Types of real-world data studies.

Figure 2. Real-world studies can help guide the management of under-represented patients

agents. These trials excluded patients with brain metastases, poor performance status, and non-clear cell RCC, and underrepresented minority patients, patients of advanced age, and others, arguably giving a skewed view of this clinical scenario.

Matrana and Marschner went on to explain that while there have been an additional 10,000+ metastatic RCC patients documented in real-world studies, there is still a paucity of data representing the "average" patient who is seen in clinical practices today. They specifically addressed different types of real world studies, from prospective expanded access programs, to single-center and registry retrospective studies and those based on payor databases. Payor databases for example, such as the IMS LifeLink Health Plan Claims Database, have allowed for analysis to examine the evolution of treatment patterns and associated costs for 1,527 metastatic RCC patients in the US between October 2003 and September 2011.

This analysis revealed that over the last years, more patients have been able to receive more lines of therapy, but treatment costs remain high. The speakers also addressed the limitations of these types of studies, particularly highlighting the fact that because assessments may not be as frequent off protocol as compared to those in a prospective trial, PFS and OS may be overestimated in real-world studies, and minor adverse events of treatment are more likely to be underrepresented in these data.

Who Are the Underrepresented Patients in Clinical Trials?

Matrana conducted a breakout session about underrepresented patients. During this session, he explained that many "average" patients are ineligible for clinical trials, and explained that patient selection criteria within trials often create bias towards good patient prognosis (**Figures 3,4**). The question was posed: If the study population is not representative of the entire treatment population, how applicable are the trial results to clinical practice? Both Heng and Marscher have shown that mRCC patients who participate in clinical trials tend to have better outcomes than those who do not. Heng, for example, analysed 2,210 from the International Metastatic RCC Database Consortium (IMDC). Of these, 768 (35%) patients were deemed ineligible for clinical trials by standard inclusion and exclusion criteria. He found that the response rate, median progression-free survival (PFS) and median overall survival of first-line targeted therapy were all significantly worsened in those patients deemed ineligible for trial.[2]

> "There are particular subgroups of RCC patients that are routinely excluded from trials; these include patients with brain metastases, non-clear cell RCC, and those with poor performance status."

There are particular subgroups of RCC patients that are routinely excluded from trials; these include patients with brain metastases, non-clear cell RCC, and those with poor performance status. Certainly, it is difficult to gather much insight regarding these patients from most clinical trials, which exclude them. Expanded access programs have given us some

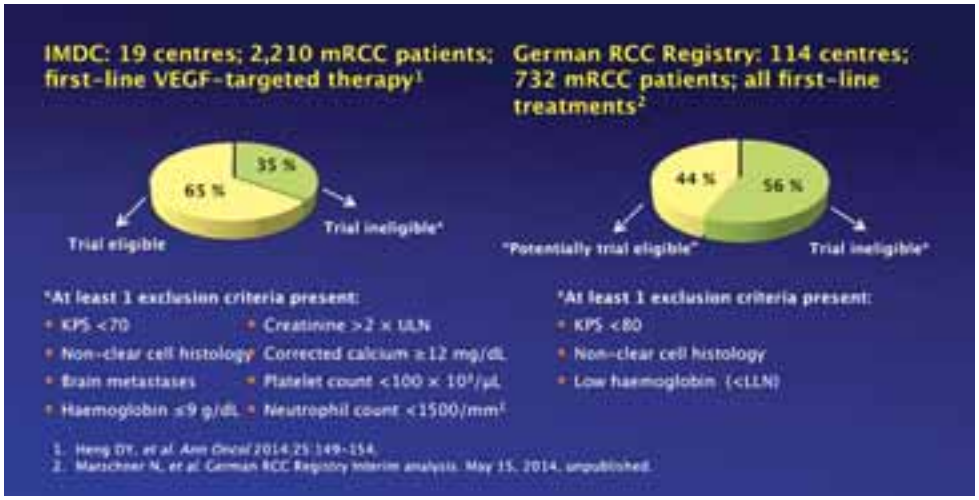

Figure 3. Trial ineligible patients have significantly worse outcome than clinical trial participants.[1,2]

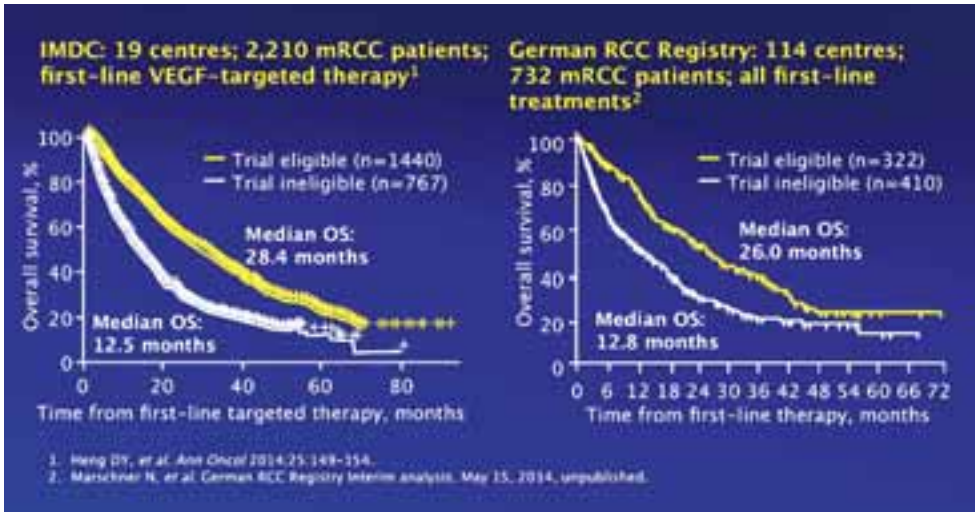

Figure 4. Overall survival in trial ineligible patients and clinical trial participants.[1,2]

prospective insight into outcomes in patients with brain metastases. For example, in the sunitinib expanded access program, median PFS for the entire population treated (n=4371) was 10.9 months (95% CI, 10.3–11.2), while the 321 patients with brain metastases within that population had a median PFS of only 5.6 months (95% CI, 5.2–6.1).[3]

In a single-center retrospective study presented at the Genitourinary Cancers Symposium in 2014, Bastos and colleagues noted that the number of brain metastases a patient has significant effect on prognosis. In their small study, they found a median OS of 20.4 months among patients with only a single brain metastasis from mRCC (n=30) compared with a median OS of 7.9 months in patients with ≥2 brain mets (n=35).

Redefining the Multi-Disciplinary Team for Newly Diagnosed RCC

A panel including Simon Chowdhury, Tom Powles, Tim O'Brien, Giles Rottenberg, and David Cullen gathered to discuss redefining the multi-disciplinary team, and specifically addressed the goal of discussing newly diagnosed RCC patients with a multi-disciplinary team (MDT). All agreed that while such discussions can be useful for treatment planning purposes, especially in complex cases, the group also cautioned that lengthy conversations that only engage one discipline amongst the team may be a poor use of the other team members' time. For example, if an MDT meeting is dominated by discussions of surgical minutia, this may not be the best use of the medical oncologist's time, while on the other hand, if the meetings largely focus on discussions of targeted therapy for metastatic disease, this may be a poor utilization of a surgeon's time. They also discussed the importance of involving nursing and mid-levels in such teams and the usefulness of a team huddle prior to clinic to discuss the day's scheduled patients and their clinical plans.

Tom Hutson of US Oncology and Baylor presented a breakdown of navigating treatment pathways. He emphasized that the most important factor in choosing a first line treatment for a patient with metastatic renal cell carcinoma is to choose the most active treatment first. He also noted that while drug labeling in the United States is often broad and US guidelines, such as the National Comprehensive Cancer Network guidelines, are also broad, this creates unique challenges because there are so many viable treatment options for practitioners to choose from. On the other hand, and many other health care delivery systems outside the United States, drug labeling is narrower and in many European countries, for example, patients may have access to only one or two lines of therapy, presenting different treatment selection challenges.

Pivotal Studies That Guide Therapy Selections

Hutson reviewed several of the seminal studies which may aid practitioners in making appropriate therapy selections. He described the RECORD-3 study in which the sequence of everolimus followed by suntinib was compared with the sequence of sunitnib followed by everolimus. Patients receiving everolimus prior to sunitinib appeared to have better outcomes (median PFS was 7.9 months for 1st-line everolimus and 10.7 months for 1st-line suninib). But, the study is designed did not indicate

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The ADAPT (**A**utologous **D**endritic Cell Immunotherapy (**A**GS-003) **P**lus Standard **T**reatment) Phase 3 study is currently investigating the combination of an autologous dendritic cell based immunotherapy, AGS-003, plus standard targeted drug therapy (initiating with, but not limited to, sunitinib). The study will compare the following outcomes between study arms: 1) Overall survival (primary endpoint), 2) PFS, response rate and safety (secondary endpoints) and 3) immunologic response (exploratory).

Patients with newly-diagnosed, synchronous metastatic RCC at presentation must meet the following key eligibility criteria:

- ≥ 18 years of age
- Newly diagnosed with metastatic RCC and no known brain metastases
- Good candidate for standard surgery (partial or cytoreductive nephrectomy)
- Good candidate to receive standard targeted drug therapy (initiating with Sunitinib)
- No autoimmune disorders (eg. RA, MS, SLE)

To learn more, please visit the ADAPT study website at www.adaptkidneycancer.com or contact the study team at clinicalteam@adapt-study.com

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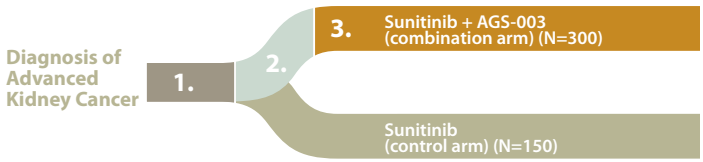

1. Surgery

(Tumor sample taken)

2. Blood Donation

(Only for patients who are assigned to the AGS-003 treatment regimen)

3. Standard Treatment with Sunitinib + AGS-003

(Begins 6-weeks after 1st dose of sunitinib)

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if everolimus issue with the most appropriate choice for second line therapy. He also described the SWITCH study, which found no difference in outcomes between patients it makes no difference whether patients with metastatic renal cell carcinoma who first started on therapy with sorafenib and then switched to sunitinib upon progression versus those who started on therapy with suninib and then switched to sorafenib. Hutson also described the INTOSECT trial, an international phase III study which he led, that compared the efficacy of temsirolimus and sorafenib as second-line therapy in patients with metastatic renal cell carcinoma who had progressed on first line sunitinib. The study found no difference in PFS between second-line temsirolimus versus sorafenib, but a longer OS was observed with sorafenib, perhaps suggesting sequenced VEGFR inhibition may benefit patients with mRCC.

New Insights on Prognostic Tools

Daniel Heng of Calgary, Alberta, Canada, spoke on prognostic tools. He noted that the most ideal prognostic tools are easy to use, utilize the most relevant disease characteristics, and accurately distinguish among varying prognostic groups. Heng described the well-known MKSCC risk-model for mRCC that was developed during the era of immunotherapy. He then went on to describe his own prognostic model for mRCC, based on data from the International mRCC Database Consortium (IMDC).[4] The Heng model builds upon the MSKCC model, integrating additional characteristics and relying on clinical data that includes patients treated in the targeted therapy era. Dr. Heng went on to describe the IMDC analysis that has shown that prognosis is dynamic. For example, those patients who were originally described as poor-risk, but who have a prolonged response to targeted therapy, often have better outcomes than intermediate risk patients, suggesting that a good-response to therapy may in fact change a patient's prognosis.

Heng described how prognostic features can help tailor treatments. Certainly, current guidelines endorse first-line temsirolimus for patients with poor–risk mRCC, but this is base on the results of one study, with few other large studies examining targeted therapies in poor-risk patients. Tannir's TemPa study, comparing temsirolimus vs pazopanib in patients with poor-risk mRCC and others will hopefully answer this question. Heng also went on to discuss the role of prognostic risk categorization in determining which patients should undergo cytoreductive nephrectomy.

He and his colleagues conducted a retrospective study comparing 982 mRCC patients who had a cytoreductive nephrectomy with 676 mRCC patients who did not. The study found that cytoreductive nephrectomy followed by targeted therapy potentially provided a meaningful overall survival benefit. However, patient selection largely based on prognostic variables was key to determining the appropriateness of this invasive surgery. Those patients who had a limited life expectancy or four or more poor prognostic risk factors based on the Heng criteria had limited if any benefit from this procedure.

How Biomarkers May Hold Key to Personalized Therapy

Thomas Powles from the Barts Cancer Institute of London and Chun-Fang Xu from GlaxoSmithKline gave a presentation on biomarkers in RCC. They began by defining the difference between prognostic biomarkers, which predict outcomes, and predictive outcomes, which may guide treatment. They stressed that biomarkers may lead us to truly personalized therapy, in which the right drug is paired with the right patient at the right time, and gave examples, such as HER2neu overexpression in breast cancer and VEGF mutations in lung cancer, which both allow for appropriate selection of treatments based on underlying biological mechanisms of disease. They noted that many potential candidate RCC biomarkers have been found, but few have progressed toward clinical utility. Most of these do not have a high sensitivity or specificity.

"Several studies have now confirmed that higher levels of PD-1 expression on RCC cells are associated with more aggressive features and worse clinical outcomes. Like Her2neu overexpression in breast cancer, efficaciously targeting PD-1 overexpression in RCC may potentially change the prognosis in this subset of patients."

Among those biomarkers that have recently garnered attention, cytokines and antigenic factors have shown to be potentially useful in RCC. Powles and Xu reviewed a study by Tran in which five candidate markers (interleukin 6, interleukin 8, hepatocyte growth factor (HGF), tissue inhibitor of metalloproteinases (TIMP)-1, and E-selectin), were analyzed in patients treated with pazopanib. These studies identified associations of these markers with continuous tumour shrinkage or PFS. This study found that patients treated with pazopanib who had high concentrations (relative to median) of interleukin 8 (P=0·006), osteopontin (P=0·0004), HGF (P=0·010), and TIMP-1 (P=0·006) had shorter PFS than did those with low concentrations. In the placebo group, high concentrations of interleukin 6 (P<0·0001), interleukin 8 (P=0·002), and osteopontin (P<0·0001) were associated with shorter PFS. Interestingly, it was found that these factors were stronger prognostic markers than the standard clinical classifications used today including the Eastern Cooperative Oncology Group classifications, and MSKCC and Heng criteria. Furthermore, the study found that high concentrations of interleukin 6 were predictive of improved relative PFS benefit from pazopanib compared with placebo.[5] In addition, several studies have now confirmed that higher levels of PD-1 expression on RCC cells are associated with more aggressive features and worse clinical outcomes. Like Her2neu overexpression in breast cancer, efficaciously targeting PD-1 overexpression in RCC may potentially change the prog-

nosis in this subset of patients.

Powles and Xu went on to describe hypertension as a biomarker. They noted that while hypertension was a good predictive factor for efficacy with VEGF-targeted TKIs, it doesn't give clinicians any information necessary to change therapy. They also noted that while VEGF expression is prognostic, it is not predictive of response to therapy, and doesn't change therapy decisions either. Among the more promising are genetic polymorphisms, which have been associated with response to targeted therapies. For example, Xu and colleagues tested several polymorphisms in patients treated with pazopanib for mRCC. They found that three polymorphisms in IL8 and HIF1A and five polymorphisms in HIF1A, NR1I2, and VEGFA showed significant association with PFS and response rates to pazopanib. Compared with the wild-type genotype, the IL8 2767TT variant genotype showed inferior PFS (27 weeks compared to 48 weeks).

The HIF1A 1790AG genotype was also associated with inferior PFS and reduced RR, compared with the wild-type genotype (median PFS, 20 v 44 weeks).[6] If validated, the researchers believe that these markers may explain why certain patients fail VEGF-targeted TKI therapy and may support the use of alternative strategies to circumvent this issue. Likewise, Powles work has shown the mutations in the VHL gene may be predictive of response in mTOR inhibitors. Ultimately, Powles and Xu concluded their information presentation by asking how realistic is it to develop a predictive biomarker for differentiating between VEGF-targeted therapies in mRCC, when most are already looking ahead at next generation immunotherapies and asking how to sequence, combine, or replace current standards of care with these newer agents. Looking forward, future biomarkers for immunotherapy will likely be even more important to find.

Conclusion

The meeting concluded with closing remarks from host Bernard Escudier. He gave a brief forward-looking talk that described many of the promises and challenges ahead in the field of mRCC. Certainly looming on the horizon, are the new immunotherapies, including PD-1 and PD-L1 inhibitors, which hold great potential to further outcomes for patients with mRCC. Many years of research will be needed to define the optimal use of these agents. Although not garnishing as much attention, cancer vaccines against mRCC are in development and preliminary results of the ADAPT study are anticipated in the near future as well. In conclusion, while block-buster targeted agents have shifted treatment paradigms in mRCC over the last decade and made an unprecedented impact on quality of life and survival, few patients are cured of mRCC, and the ultimate goal of complete disease eradication should not be deferred.

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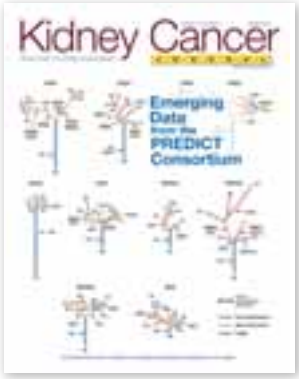

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spond to IL-2. Similarly, additional work is focusing on the extent to which predictive markers can be identified for other treatment strategies.

The nature and extent of that challenge becomes real through the image on the cover. The image is somewhat haunting because within it lies much of the enigma of the disease still to be revealed. But slowly, like the layers of an onion being peeled away, the essence of the disease, or at least glimmers of it, will be delineated.

Janice P. Dutcher, MD
Guest Editor

RCC (ccRCC) and tumor-infiltrating lymphocytes (TILs), and its expression levels in cancer cells and TILs correlated with the pathological tumor stage and histological grade. Analysis revealed that the strong expression of AhR in cancer cells was a significant and independent predictor of disease-specific survival. AhR ligands up-regulated the expression of AhR and CYPs and promoted invasion by up-regulating MMPs. Furthermore, siRNA for AhR down-reg- ulated CYPs, and inhibited cancer cell invasion together with the down-regulation of MMPs.
Conclusion: These results suggest that AhR regulates the invasion of ccRCC and may be involved in tumor immunity. Therefore, inhibiting the activation of AhR may represent a potentially attractive therapeutic target for ccRCC patients.

RSUME inhibits VHL and regulates its tumor suppressor function. Gerez J, Tedesco L, Bonfiglio JJ, et al. *Oncogene*. 2014 Dec 15;0. doi: 10.1038/onc.2014.407. [Epub ahead of print]
Summary: Recently described mechanisms for pVHL modulation shed light on the open question of the HIF/pVHL pathway regulation, essential for tumor growth.. This study determined the molecular mechanism by which RSUME stabilizes HIFs, by studying RSUME effect on pVHL function and determined the role of RSUME on pVHL-related tumor progression. It determined that RSUME sumoylates and physically interacts with pVHL and negatively regulates the assembly of the complex between pVHL, Elongins and Cullins (ECV), inhibiting HIF-1 and 2 ubiquitination and degradation. RSUME is expressed in human VHL tumors (renal clear-cell carcinoma (RCC), pheochromocytoma and hemangioblastoma) and by overexpressing or silencing RSUME in a pVHL-HIF-oxygen-dependent degradation stability reporter assay, the authors determined that RSUME is necessary for the loss of function of type 2 pVHL mutants. The functional RSUME/pVHL interaction in VHL-related tumor progression was further confirmed using a xenograft assay in nude mice. RCC clones, in which RSUME was knocked down and expressed either pVHL wt or type 2 mutation, had an impaired tumor growth, as well as HIF-2 , vascular endothelial growth factor A and tumor vascularization diminution.
Conclusion: This work shows a novel mechanism for VHL tumor progression and presents a new mechanism and factor for targeting tumor-related pathologies with pVHL/HIF altered function.

Pre-existing type 2 diabetes mellitus is an independent risk factor for mortality and progression in patients with renal cell carcinoma. Vavallo A, Simone S, Lucarelli G, et al. *Medicine*. 2014 Dec;93(27):e183. doi: 10.1097/MD.
Summary: This report investigated whether type 2 diabetes mellitus (T2DM) may influence the overall survival (OS), cancer-specific survival (CSS), and progression-free survival (PFS) in patients with surgically treated RCC. Medical records of 924 patients treated by radical or partial nephrectomy for sporadic, unilateral RCC were reviewed. Patients with type-1 DM and with T2 DM receiving insulin treatment were excluded. Of the 924 RCC patients, 152 (16.5%) had T2DM. Mean follow-up was 68.5 months. Mean OS was 41.3 and 96.3 months in T2DM and non-T2DM patients, respectively (P<0.0001).The estimated CSS rates at 1, 3, and 5 years in T2DM versus non-T2DM patients were 63.4% versus 76.7%, 30.4% versus 56.6%, and 16.3% versus 48.6%, respectively (P=0.001). Mean PFS was significantly lower (31.5 vs 96.3 months; P<0.0001) in the T2DM group. At multivariate analysis, T2DM was an independent adverse prognostic factor for OS (hazard ratio [HR]=3.44; CSS (HR=6.39; and PFS (HR=4.71.)
Conclusion: Patients with RCC and pre-existing T2DM have a shorter OS, increased risk of recurrence, and higher risk for kidney cancer mortality than those without diabetes.

Health-related quality of life, personality and choice of coping are related in renal cell carcinoma patients. Beisland E, Beisland C, Hjelle KM, et al. *Scand J Urol*. 2014 Dec 17:1-8. [Epub ahead of print].
Summary: Health-related quality of life (HRQoL) was determined by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), personality by the Eysenck Personality Inventory and coping by the COPE Questionnaire. Given tumor treatment, TNM stage and patient-reported comorbidity were also determined. The HRQoL indices were also summarized in general quality of life/health, functional sum and symptom sum scores. EORTC C30 sum scores were negatively associated with the personality trait of neuroticism [common variance (CV) 19-36%]. Avoidant choice of coping inversely accounted for 9-18% of the total HRQoL variance, while reported coping by humor

(continued on page 140)

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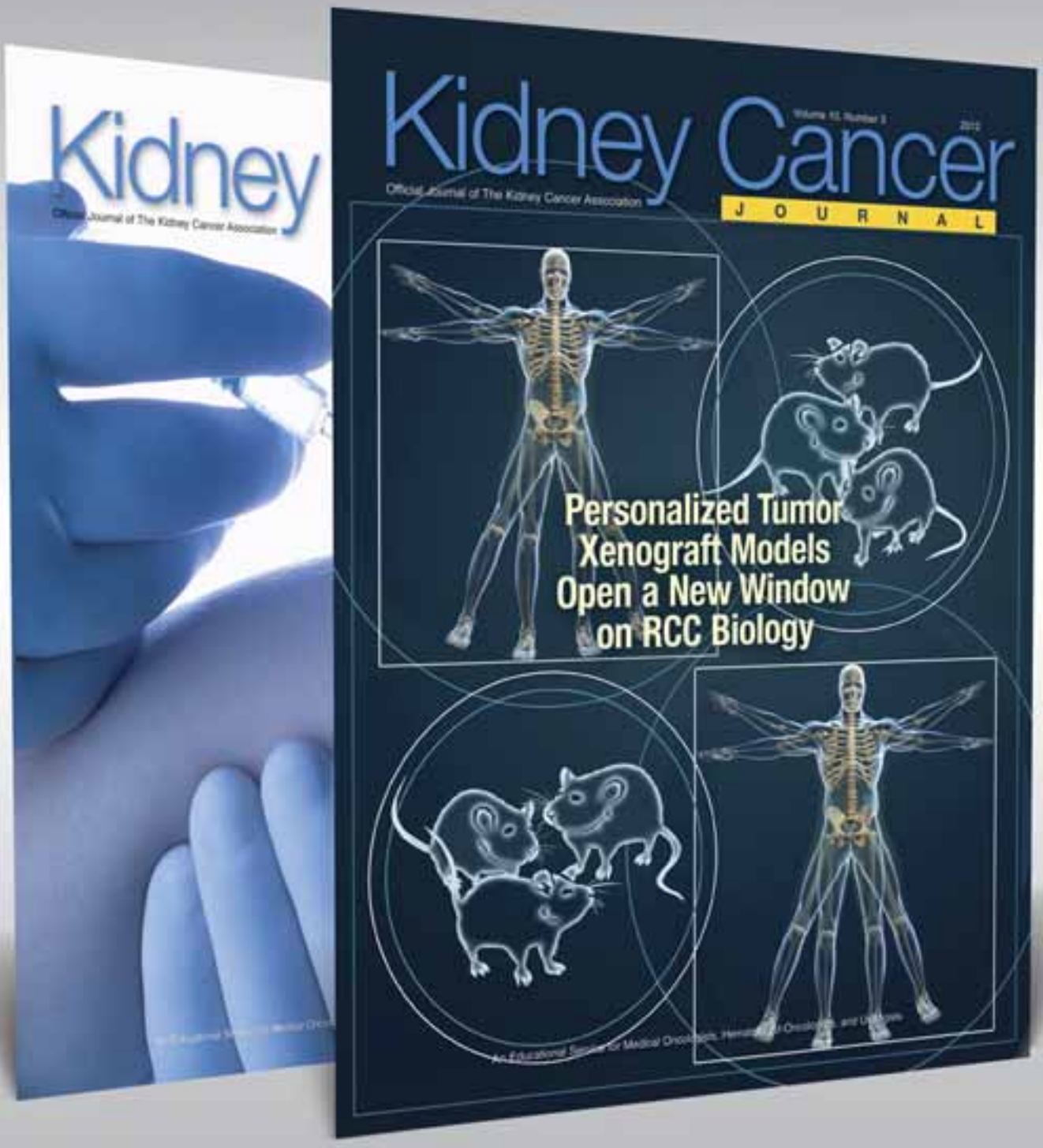


JOURNAL CLUB *(continued from page 138)*

was to some extent negatively associated with HRQoL score (CV_{max} 4%). Indeed, all of the quality of life indices except for one were significantly negatively correlated with neuroticism and avoidance coping. Patients with low HRQoL due to treatment, secondary to flank or open surgery, reported a closer association between problem-focused choice of coping and HRQoL than the other patients. Moreover, present comorbidities were uniquely associated with a lowered HRQoL.
Conclusion: HRQoL is related to treatment-related factors in RCC patients, but shown here to be more strongly associated with psychological factors and present comorbidity. These findings suggest that attention should be paid to supportive treatment of RCC patients.

Preoperative predictors of malignancy and unfavorable pathology for clinical T1a tumors treated with partial nephrectomy: A multi-institutional analysis. **Ball MW, Gorin MA, Bhayani SB, et al. *Urol Oncol*. 2014 Dec 10. pii: S1078-1439(14)00364-0. doi:10.1016/j.urolonc.2014.11.003. [Epub ahead of print]**
Summary: PN records from 5 centers were retrospectively queried for patients with a clinically localized single tumor <4cm on imaging (clinical T1a). Between 2007 and 2013, 1,009 patients met the inclusion criteria. Unfavorable pathology was defined as any grade III or IV RCC or tumors upstaged to pathologic T3a disease. Logistic regression models were used to determine preoperative characteristics associated with RCC and with unfavorable pathology. A total of 771 (76.4%) patients were found to have RCC and 198 (19.6%) had unfavorable pathology. Factors associated with the presence of malignancy were imaging tumor size≥3cm (odds ratio [OR] = 1.46; $P = 0.040$), male sex (OR = 1.88; $P<0.0001$), and nephrometry score≥8 (OR = 1.64; $P = 0.005$). These same factors were independently associated with risk of unfavorable pathology: size≥3cm (OR = 1.46; $P = 0.021$), male sex (OR = 2.35; $P<0.0001$), and nephrometry score≥8 (OR = 1.49; $P = 0.015$). The c statistic was 0.62 for the predicting malignancy and 0.63 for unfavorable pathology.
Conclusion: In this multi-institutional cohort, male sex, imaging tumor size≥3cm, and nephrometry score≥8 were predictors of RCC and adverse pathology following PN. These factors may assist in risk stratification and selective renal mass biopsy before decision making. Further studies are necessary to validate these findings.

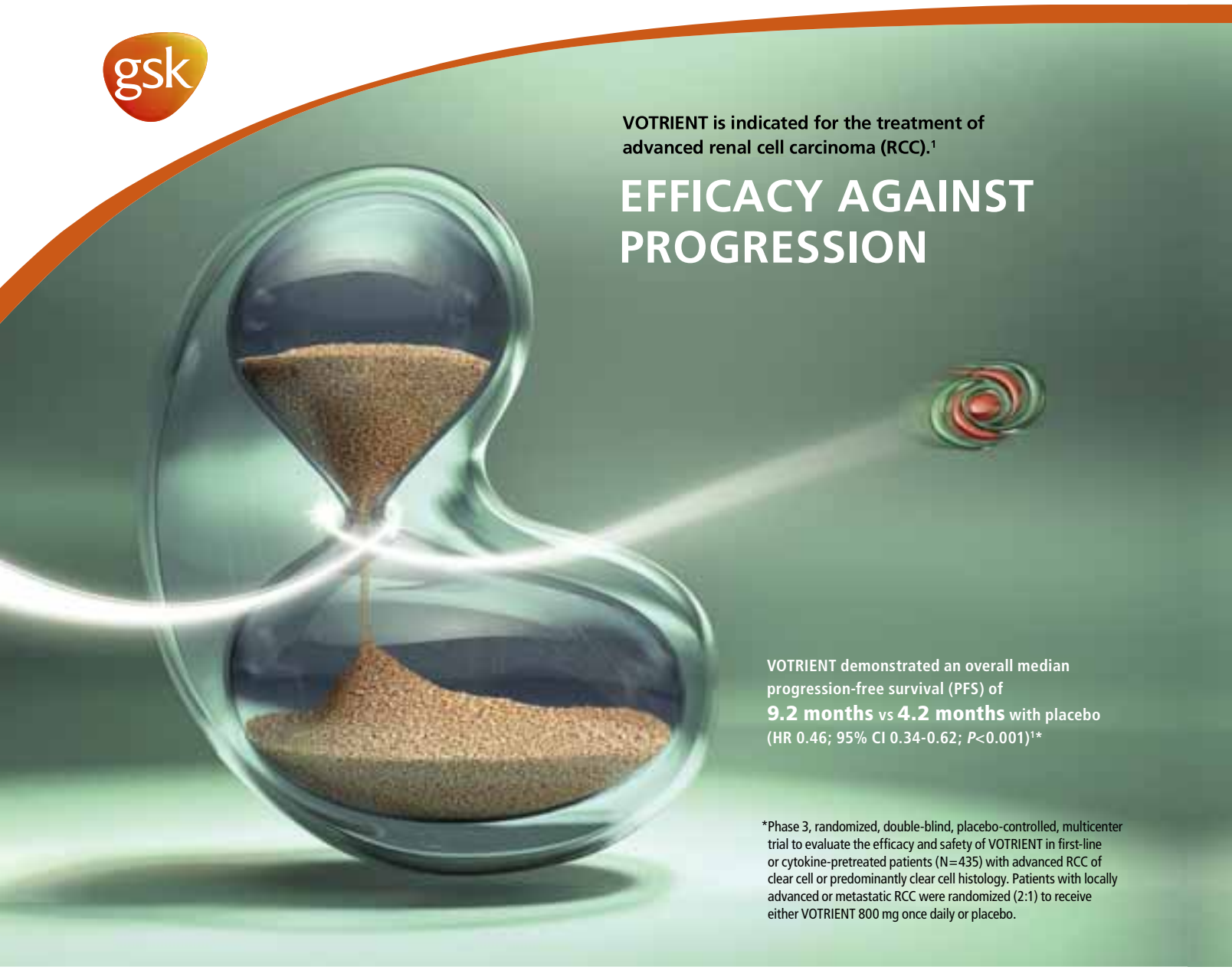
Regulatory T cells and TGF-β1 in clinically localized renal cell carcinoma: Comparison with age-matched healthy controls. **Kim CS, Kim Y, Kwon T, et al. *Urol Oncol*. 2014 Dec 10. pii: S1078-1439(14)00365-2. doi: 10.1016/j.urolonc.2014.11.004. [Epub ahead of print]**
Summary: The proportion of Treg cells in the peripheral blood (PB) of 59 patients with clinically localized RCC and 65 healthy controls (HCs), as well as the prevalence of Treg cells among TILs and lymphocytes in normal kidney tissue, were evaluated by flow cytometry using specific monoclonal antibodies recognizing $CD4^+$, $CD25^+$, and $Foxp3^+$ markers. In addition, the levels of transforming growth factor (TGF)-β1, interleukin-6, tumor necrosis factor-α, and interferon-γ were determined using standard enzyme-linked immunosorbent assay. There was no difference between the mean percentage of Treg cells in the PB of patients with RCC and HCs ($P = 0.148$). However, the proportion of Treg cells showed a significant positive correlation with tumor size (r = 0.295, $P = 0.029$), with the percentage of PB Treg cells significantly higher in patients with RCC with large tumors (≥7cm) than in HCs (4.6±5.8% vs. 1.9±2.6%, $P = 0.023$). There was no statistically significant difference in the percentage of Treg cells among TILs and lymphocytes in normal kidney tissue ($P = 0.629$). The mean TGF-β1 level in patients with RCC was statistically significantly higher than in HCs ($P<0.001$).
Conclusion: In this study, there was evidence for an increased proportion of Treg cells in the PB of clinically localized patients with RCC with substantial tumor burden and a higher level of TGF-β1 compared with age-matched HCs. KCJ

MEDICAL INTELLIGENCE *(continued from page 123)*

group had advanced sporadic (non-hereditary) pRCC. Nineteen of the patients had received at least one previous systemic therapy, such as sunitinib, that had not been successful in preventing their disease progressing.

Dr Srinivasan reported "Almost all the patients with HLRCC responded with their tumors either shrinking or remaining stable and not progressing. There was an overall response rate of 65%, with 13 patients showing tumor shrinkage of more than 30% and seven patients with stable disease. Many of the responses were long-lasting; some of the patients have remained on the study for three years or more, which is a significant since metastatic HLRCC is uniformly fatal and patients usually die within a year or so. Approximately a third of the patients with sporadic pRCC showed very good partial responses, many of which were durable. There was an overall response rate of 29%, with tumours shrinking in six patients and 12 patients with stable disease."

The median progression-free survival among HLRCC patients was 24.2 months, while for the sporadic pRCC patients it was 7.4 months. This compares well with existing times for patients on other treatments. "The median progression-free survival for metastatic pRCC appears to be less than six months with most regimens commonly used today," Dr Srinivasan said. "This is also true for patients with metastatic HLRCC, who generally demonstrate rapidly progressive fatal disease." KCJ



VOTRIENT is indicated for the treatment of advanced renal cell carcinoma (RCC).[1]

EFFICACY AGAINST PROGRESSION

VOTRIENT demonstrated an overall median progression-free survival (PFS) of **9.2 months** vs **4.2 months** with placebo (HR 0.46; 95% CI 0.34-0.62; *P*<0.001)[1]*

*Phase 3, randomized, double-blind, placebo-controlled, multicenter trial to evaluate the efficacy and safety of VOTRIENT in first-line or cytokine-pretreated patients (N=435) with advanced RCC of clear cell or predominantly clear cell histology. Patients with locally advanced or metastatic RCC were randomized (2:1) to receive either VOTRIENT 800 mg once daily or placebo.

Important Safety Information for VOTRIENT

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

- **Hepatic Toxicity and Hepatic Impairment:** Severe and fatal hepatotoxicity has occurred. Increases in serum transaminase levels (ALT, AST) and bilirubin were observed. Transaminase elevations occur early in the course of treatment (92.5% of all transaminase elevations of any grade occurred in the first 18 weeks). In patients with pre-existing moderate hepatic impairment, the starting dose of VOTRIENT should be reduced to 200 mg per day or alternatives to VOTRIENT should be considered. Treatment with VOTRIENT is not recommended in patients with severe hepatic impairment. Concomitant use of VOTRIENT and simvastatin increases the risk of ALT elevations and should be undertaken with caution *[see* **Drug Interactions***]*. 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 occurred. Use with caution in patients with a history of QT interval prolongation, 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.

Please see additional Important Safety Information for VOTRIENT on subsequent pages.
Please see Brief Summary of Prescribing Information, including Boxed Warning, for VOTRIENT on adjacent pages.

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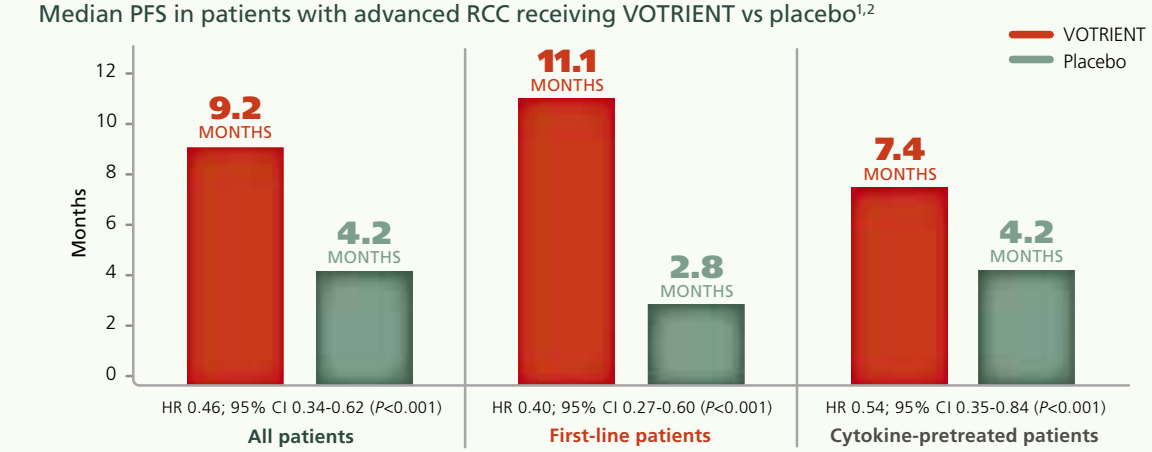
pazopanib tablets (200 mg)

EFFICACY LIGHTS THE WAY

VOTRIENT® (pazopanib) is indicated for the treatment of patients with advanced renal cell carcinoma (RCC).[1]

VOTRIENT: Significant PFS improvement in patients with advanced RCC[1]



Randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of VOTRIENT in patients (N=435) with advanced RCC. Patients with locally advanced or metastatic RCC of clear cell or predominantly clear cell histology were randomized (2:1) to receive either VOTRIENT 800 mg (n=290) once daily or placebo (n=145). The study included first-line patients receiving VOTRIENT (n=155) or placebo (n=78) as well as cytokine-pretreated patients receiving VOTRIENT (n=135) or placebo (n=67).[1]

Important Safety Information for VOTRIENT (cont'd)

- **Cardiac Dysfunction:** Cardiac dysfunction, such as congestive heart failure and decreased left ventricular ejection fraction (LVEF), has occurred. In the overall safety population for RCC (N=586), cardiac dysfunction was observed in 4/586 patients (0.6%). Monitor blood pressure and manage promptly using a combination of anti-hypertensive therapy and dose modification of VOTRIENT (interruption and re-initiation at a reduced dose based on clinical judgment). Carefully monitor patients for clinical signs or symptoms of congestive heart failure. Baseline and periodic evaluation of LVEF is recommended in patients at risk of cardiac dysfunction, including previous anthracycline exposure.
- **Hemorrhagic Events:** Fatal hemorrhagic events were reported in 0.9% (5/586) of patients in the RCC trials. In the randomized RCC trial, 13% (37/290) of patients treated with VOTRIENT compared to 5% (7/145) of patients on placebo experienced at least 1 hemorrhagic event. The most common hemorrhagic events were hematuria (4%), epistaxis (2%), hemoptysis (2%), and rectal hemorrhage (1%). VOTRIENT should not be used in patients who have a history of hemoptysis, cerebral, or clinically significant gastrointestinal hemorrhage in the past 6 months.
- **Arterial Thromboembolic Events:** Arterial thromboembolic events have been observed, including fatal events (0.3%, 2/586) in the RCC trials. In the randomized RCC trial, 2% (5/290) of patients receiving VOTRIENT experienced myocardial infarction or ischemia, 0.3% (1/290) had a cerebrovascular accident, and 1% (4/290) had an event of transient ischemic attack. No arterial thromboembolic events were reported in patients who received placebo. Use with caution in patients who are at increased risk for these events and do not use in patients who have had an arterial thromboembolic event in the past 6 months.
- **Venous Thromboembolic Events:** Venous thromboembolic events (VTEs) have occurred, including venous thrombosis and fatal pulmonary emboli. In the randomized RCC trial, VTEs were reported in 1% of patients treated with VOTRIENT and in 1% of patients treated with placebo. Monitor for signs and symptoms.
- **Thrombotic Microangiopathy:** Thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) has been reported in clinical trials of VOTRIENT as monotherapy, in combination with bevacizumab, and in combination with topotecan. VOTRIENT is not indicated for use in combination with other agents. Six of the 7 TMA cases occurred within 90 days of the initiation of VOTRIENT. Improvement of TMA was observed after treatment was discontinued. Monitor for signs and symptoms of TMA. Permanently discontinue VOTRIENT in patients developing TMA. Manage as clinically indicated.
- **Gastrointestinal Perforation and Fistula:** In RCC trials, gastrointestinal perforation or fistula were reported in 0.9% (5/586) of patients receiving VOTRIENT. Fatal perforation events occurred in 0.3% (2/586) of these patients. Use with caution in patients at risk for these events and monitor for signs and symptoms.
- **Reversible Posterior Leukoencephalopathy Syndrome (RPLS):** RPLS has been reported and may be fatal. Permanently discontinue VOTRIENT in patients developing RPLS.
- **Hypertension:** Hypertension, including hypertensive crisis, has occurred in clinical trials. Hypertension occurs early in the course of treatment (approximately 40% of cases occurred by Day 9 and 90% of cases occurred in the first 18 weeks). Blood pressure should be well-controlled prior to initiating VOTRIENT, monitored early after starting treatment (no longer than 1 week), and frequently thereafter. Treat increased blood pressure promptly with standard anti-hypertensive therapy and dose reduction or interruption of VOTRIENT as clinically warranted. Discontinue VOTRIENT if there is evidence of hypertensive crisis or if hypertension is severe and persistent despite anti-hypertensive therapy and dose reduction of VOTRIENT. Approximately 1% of patients required permanent discontinuation of VOTRIENT because of hypertension.
- **Wound Healing:** VOTRIENT may impair wound healing. Interruption of therapy is recommended in patients undergoing surgical procedures; treatment with VOTRIENT should be stopped at least 7 days prior to scheduled surgery. VOTRIENT should be discontinued in patients with wound dehiscence.
- **Hypothyroidism:** Hypothyroidism was reported in 7% (19/290) of patients treated with VOTRIENT in the randomized RCC trial and in no patients receiving placebo. Monitoring of thyroid function tests is recommended.
- **Proteinuria:** In the randomized RCC trial, proteinuria was reported as an adverse reaction in 9% (27/290) of patients receiving VOTRIENT, leading to discontinuation of treatment in 2 patients. There were no reports of proteinuria in patients receiving placebo. Monitor urine protein. Interrupt treatment for 24-hour urine protein ≥3 grams and discontinue for repeat episodes despite dose reductions.
- **Infection:** Serious infections (with or without neutropenia), some with fatal outcomes, have been reported. Monitor for signs and symptoms and treat active infection promptly. Consider interruption or discontinuation of VOTRIENT.
- **Increased Toxicity with Other Cancer Therapy:** VOTRIENT is not indicated for use in combination with other agents. Increased toxicity and mortality have been observed in clinical trials administering VOTRIENT in combination with lapatinib or with pemetrexed. The fatal toxicities observed included pulmonary hemorrhage, gastrointestinal hemorrhage, and sudden death. A safe and effective combination dose has not been established with these regimens.
- **Increased Toxicity in Developing Organs:** The safety and effectiveness of VOTRIENT in pediatric patients have not been established. VOTRIENT is not indicated for use in pediatric patients. Animal studies have demonstrated pazopanib can severely affect

Once-daily oral dosing[1]

- The recommended starting dose of VOTRIENT is 800 mg once daily without food (at least 1 hour before or 2 hours after a meal). Daily dose should not exceed 800 mg
- Do not crush tablets due to the potential for increased rate of absorption, which may affect systemic exposure
- If a dose is missed, it should not be taken if it is less than 12 hours until the next dose
- In advanced RCC, initial dose reduction should be 400 mg, and additional dose decrease or increase should be in 200-mg steps based on individual tolerability
- In the Phase 3 advanced RCC trial, 42% of patients on VOTRIENT required a dose interruption; 36% of patients on VOTRIENT were dose reduced
- No dose adjustment is required in patients with mild hepatic impairment
- In patients with moderate hepatic impairment, alternatives to VOTRIENT should be considered. If VOTRIENT is used in patients with moderate hepatic impairment, the dose should be reduced to 200 mg per day
- Treatment with VOTRIENT is not recommended in patients with severe hepatic impairment
- Monitor serum liver tests before initiation of treatment and at Weeks 3, 5, 7, and 9. Thereafter, monitor at Month 3 and at Month 4, and as clinically indicated. Periodic monitoring should then continue after Month 4
- **For additional information on dosing modifications based on drug interactions, please see Sections 2.2 and 7 of accompanying Brief Summary of Prescribing Information**

VOTRIENT: Summary of serious and common adverse reactions[1]

- **Severe and fatal hepatotoxicity has been observed in clinical trials. Monitor hepatic function and interrupt, reduce, or discontinue dosing as recommended**
- **Serious adverse reactions with VOTRIENT included** hepatotoxicity, QT prolongation and torsades de pointes, cardiac dysfunction, hemorrhagic events, arterial and venous thromboembolic events, thrombotic microangiopathy, gastrointestinal perforation and fistula, reversible posterior leukoencephalopathy syndrome, hypertension, impaired wound healing, hypothyroidism, proteinuria, infection, increased toxicity with other cancer therapies, increased toxicity in developing organs, and fetal harm
- **Most common adverse reactions (≥20%)** observed in patients with advanced RCC taking VOTRIENT were diarrhea, hypertension, hair color changes (depigmentation), nausea, anorexia, and vomiting

Please see additional Important Safety Information for VOTRIENT on adjacent pages.

Please see Brief Summary of Prescribing Information, including Boxed Warning, for VOTRIENT on adjacent pages.

Pazopanib (VOTRIENT®) has a Category 1 recommendation as a first-line therapy in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for relapsed or Stage IV unresectable RCC of predominant clear cell histology.[3] NCCN Guidelines® also include therapies other than pazopanib (VOTRIENT®) as first-line treatment options.

Important Safety Information for VOTRIENT (cont'd)

organ growth and maturation during early post-natal development, and resulted in toxicity to the lungs, liver, heart, and kidney and in death. VOTRIENT may potentially cause serious adverse effects on organ development in pediatric patients, particularly in patients younger than 2 years of age.

- **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.
- **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.
- **Lipase Elevations:** In a single-arm RCC trial, increases in lipase values were observed for 27% (48/181) of patients. In the RCC trials of VOTRIENT, clinical pancreatitis was observed in <1% (4/586) of patients.
- **Pneumothorax:** Two of 290 patients treated with VOTRIENT and no patients on the placebo arm in the randomized RCC trial developed a pneumothorax.
- **Bradycardia:** In the randomized trial of VOTRIENT for the treatment of RCC, bradycardia based on vital signs (<60 beats per minute) was observed in 19% (52/280) of patients treated with VOTRIENT and in 11% (16/144) of patients on the placebo arm.
- **Drug Interactions:** Coadministration with strong CYP3A4 Inhibitors (eg, ketoconazole, ritonavir, clarithromycin) increases concentrations of pazopanib and should be avoided, but, if warranted, reduce the dose of VOTRIENT to 400 mg. Avoid grapefruit and grapefruit juice.

  Concomitant use of strong CYP3A4 inducers (eg, rifampin) should be avoided due to the potential to decrease concentrations of pazopanib. VOTRIENT should not be used in patients who cannot avoid chronic use of CYP3A4 inducers.

  Concomitant treatment with strong inhibitors of Pgp or breast cancer resistance protein (BCRP) should be avoided due to risk of increased exposure to pazopanib.

  CYP Substrates: 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.

  Concomitant use of VOTRIENT and simvastatin increases the incidence of ALT elevations. If a patient develops ALT elevations, follow dosing guidelines for VOTRIENT, consider alternatives to VOTRIENT, or consider discontinuing simvastatin. There are insufficient data to assess the risk of concomitant administration of alternative statins and VOTRIENT.

  Drugs That Raise Gastric pH: Avoid concomitant use of VOTRIENT with drugs that raise gastric pH (eg, esomeprazole) due to the potential to decrease concentrations of pazopanib. Consider short-acting antacids in place of proton pump inhibitors (PPIs) and H2 receptor antagonists. Separate antacid and pazopanib dosing by several hours.
- **Adverse Reactions in the Randomized RCC Trial:** Forty-two percent of patients on VOTRIENT required a dose interruption. Thirty-six percent of patients on VOTRIENT were dose reduced.

  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 patients taking VOTRIENT 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%); and leukopenia (37% vs 6%), neutropenia (34% vs 6%), thrombocytopenia (32% vs 5%), and lymphocytopenia (31% vs 24%).

References: 1. VOTRIENT® (pazopanib) Tablets [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2014. **2.** Sternberg CN, et al. *J Clin Oncol.* 2010;28(6):1061-1068. **3.** Referenced with permission from The NCCN Clinical Practice Guidelines in Oncology® for Kidney Cancer V3.2014. ©National Comprehensive Cancer Network, Inc. 2014. All rights reserved. Accessed April 30, 2014. To view the most recent and complete version of the guideline, go online to www.nccn.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN content are trademarks owned by the National Comprehensive Cancer Network, Inc.

Please see additional Important Safety Information for VOTRIENT on adjacent pages.

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Votrient®
pazopanib tablets (200 mg)

EFFICACY LIGHTS THE WAY

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 trials. 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 starting 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:** In RCC, the initial dose reduction should be 400 mg, and additional dose decrease or increase should be in 200 mg steps based on individual tolerability. Hepatic Impairment: No dose adjustment is required in patients with mild hepatic impairment. In patients with moderate hepatic impairment, alternatives to VOTRIENT should be considered. If VOTRIENT is used in patients with moderate hepatic impairment, the dose should be reduced to 200 mg per day. VOTRIENT is not recommended in patients with severe hepatic impairment *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3) of full prescribing information]*. Concomitant Strong CYP3A4 Inhibitors: The concomitant use of strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir, clarithromycin) increases pazopanib concentrations and should be avoided. Consider an alternate concomitant medication with no or minimal potential to inhibit CYP3A4. 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 *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3) of full prescribing information]*. Concomitant Strong CYP3A4 Inducer: The concomitant use of strong CYP3A4 inducers (e.g., rifampin) may decrease pazopanib concentrations and should be avoided. Consider an alternate concomitant medication with no or minimal enzyme induction potential. VOTRIENT should not be used in patients who cannot avoid chronic use of strong CYP3A4 inducers *[see Drug Interactions (7.1)]*.

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS
5.1 Hepatic Toxicity and Hepatic Impairment: In clinical trials with VOTRIENT, hepatotoxicity, manifested as increases in serum transaminases (ALT, AST) and bilirubin, was observed. 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) *[see Dosage and Administration (2.2)]*. In the randomized RCC trial, 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 2% (5/290) of patients on VOTRIENT and 1% (2/145) on placebo. Two-tenths percent of the patients (2/977) from trials that supported the RCC indication died with disease progression and hepatic failure. Monitor serum liver tests before initiation of treatment with VOTRIENT and at Weeks 3, 5, 7, and 9. Thereafter, monitor at Month 3 and at Month 4, and as clinically indicated. Periodic monitoring should then continue after Month 4. 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. Concomitant use of VOTRIENT and simvastatin increases the risk of ALT elevations and should be undertaken with caution and close monitoring *[see Drug Interactions (7.4)]*. Insufficient data are available to assess the risk of concomitant administration of alternative statins and VOTRIENT. In patients with pre-existing moderate hepatic impairment, the starting dose of VOTRIENT should be reduced or alternatives to VOTRIENT should be considered. Treatment with VOTRIENT is not recommended in patients with pre-existing severe hepatic impairment, defined as total bilirubin >3 X ULN with any level of ALT *[see Dosage and Administration (2.2), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3) of full prescribing information]*. **5.2 QT Prolongation and Torsades de Pointes:** In the RCC trials of VOTRIENT, QT prolongation (≥500 msec) was identified on routine electrocardiogram monitoring in 2% (11/558) of patients. Torsades de pointes occurred in <1% (2/977) of patients who received VOTRIENT in the monotherapy trials. In the randomized RCC trial, 1% (3/290) of patients who received VOTRIENT had post-baseline values between 500 to 549 msec. None of the 145 patients who received placebo on the trial 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 Cardiac Dysfunction:** In clinical trials with VOTRIENT, events of cardiac dysfunction such as decreased left ventricular ejection fraction (LVEF) and congestive heart failure have occurred. In the overall safety population for RCC (N=586), cardiac dysfunction was observed in 0.6% (4/586) of patients without routine on-study LVEF monitoring. Blood pressure should be monitored and managed promptly using a combination of anti-hypertensive therapy and dose modification of VOTRIENT (interruption and re-initiation at a reduced dose based on clinical judgment) *[see Warnings and Precautions (5.10)]*. Patients should be carefully monitored for clinical signs or symptoms of congestive heart failure. Baseline and periodic evaluation of LVEF is recommended in patients at risk of cardiac dysfunction including previous anthracycline exposure. **5.4 Hemorrhagic Events:** Fatal hemorrhage occurred in 0.9% (5/586) in the RCC trials. In the randomized RCC trial, 13% (37/290) of patients treated with VOTRIENT and 5% (7/145) of patients 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 of 37 patients treated with VOTRIENT who had hemorrhagic events experienced serious events including pulmonary, gastrointestinal, and genitourinary hemorrhage. One percent (4/290) of patients treated with VOTRIENT died from hemorrhage compared with no (0/145) patients on placebo. In the overall safety population in RCC (N=586), cerebral/intracranial hemorrhage was observed in <1% (2/586) of patients treated with VOTRIENT. 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. **5.5 Arterial Thromboembolic Events:** Fatal arterial thromboembolic events were observed in 0.3% (2/586) of patients in the RCC trials. In the randomized RCC trial, 2% (5/290) of patients receiving VOTRIENT experienced myocardial infarction or ischemia, 0.3% (1/290) had a cerebrovascular accident and 1% (4/290) had an event of transient ischemic attack. No arterial thromboembolic events were reported in patients who received placebo. 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 arterial thromboembolic event within the previous 6 months and should not be used in those patients. **5.6 Venous Thromboembolic Events:** In trials of VOTRIENT, venous thromboembolic events (VTE) including venous thrombosis and fatal pulmonary embolus (PE) have occurred. In the randomized RCC trial, the rate of venous thromboembolic events was 1% in both arms. There were no fatal pulmonary emboli in the RCC trial. Monitor for signs and symptoms of VTE and PE. **5.7 Thrombotic Microangiopathy:** Thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) has been reported in clinical trials of VOTRIENT as monotherapy, in combination with bevacizumab, and in combination with topotecan. VOTRIENT is not indicated for use in combination with other agents. Six of the 7 TMA cases occurred within 90 days of the initiation of VOTRIENT. Improvement of TMA was observed after treatment was discontinued. Monitor for signs and symptoms of TMA. Permanently discontinue VOTRIENT in patients developing TMA. Manage as clinically indicated. **5.8 Gastrointestinal Perforation and Fistula:** In the RCC trials, gastrointestinal perforation or fistula occurred in 0.9% (5/586) of patients receiving VOTRIENT. Fatal perforations occurred in 0.3% (2/586) of these patients in the RCC trials. Monitor for signs and symptoms of gastrointestinal perforation or fistula. **5.9 Reversible Posterior Leukoencephalopathy Syndrome:** Reversible Posterior Leukoencephalopathy Syndrome (RPLS) has been reported in patients receiving VOTRIENT and may be fatal. RPLS is a neurological disorder which can present with headache, seizure, lethargy, confusion, blindness, and other visual and neurologic disturbances. Mild to severe hypertension may be present. The diagnosis of RPLS is optimally confirmed by magnetic resonance imaging. Permanently discontinue VOTRIENT in patients developing RPLS.

5.10 Hypertension: In clinical trials, hypertension (systolic blood pressure ≥150 or diastolic blood pressure ≥100 mm Hg) and hypertensive crisis were observed in patients treated with VOTRIENT. Blood pressure should be well controlled prior to initiating VOTRIENT. Hypertension occurs early in the course of treatment (40% of cases occurred by Day 9 and 90% of cases occurred in the first 18 weeks). Blood pressure should be monitored early after starting treatment (no longer than one week) and frequently thereafter to ensure blood pressure control. Approximately 40% of patients who received VOTRIENT experienced hypertension. Grade 3 hypertension was reported in 4% to 7% of patients receiving VOTRIENT *[see Adverse Reactions (6.1)]*. Increased blood pressure should be treated promptly with standard anti-hypertensive therapy and dose reduction or interruption of VOTRIENT as clinically warranted. VOTRIENT should be discontinued if there is evidence of hypertensive crisis or if hypertension is severe and persistent despite anti-hypertensive therapy and dose reduction. Approximately 1% of patients required permanent discontinuation of VOTRIENT because of hypertension *[see Dosage and Administration (2.2)]*. **5.11 Wound Healing:** No formal trials 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. **5.12 Hypothyroidism:** Hypothyroidism, confirmed based on a simultaneous rise of TSH and decline of T4, was reported in 7% (19/290) of patients treated with VOTRIENT in the randomized RCC trial. No patients on the placebo arm had hypothyroidism. In RCC trials of VOTRIENT, hypothyroidism was reported as an adverse reaction in 4% (26/586) of patients. Proactive monitoring of thyroid function tests is recommended. **5.13 Proteinuria:** In the randomized RCC trial, proteinuria was reported as an adverse reaction in 9% (27/290) of patients receiving VOTRIENT and in no patients receiving placebo. In 2 patients, proteinuria led to discontinuation of treatment with VOTRIENT. Baseline and periodic urinalysis during treatment is recommended with follow up measurement of 24-hour urine protein as clinically indicated. Interrupt VOTRIENT and dose reduce for 24-hour urine protein ≥3 grams; discontinue VOTRIENT for repeat episodes despite dose reductions *[see Dosage and Administration (2.2)]*. **5.14 Infection:** Serious infections (with or without neutropenia), including some with fatal outcome, have been reported. Monitor patients for signs and symptoms of infection. Institute appropriate anti-infective therapy promptly and consider interruption or discontinuation of VOTRIENT for serious infections. **5.15 Increased Toxicity with Other Cancer Therapy:** VOTRIENT is not indicated for use in combination with other agents. Clinical trials of VOTRIENT in combination with pemetrexed and lapatinib were terminated early due to concerns over increased toxicity and mortality. The fatal toxicities observed included pulmonary hemorrhage, gastrointestinal hemorrhage, and sudden death. A safe and effective combination dose has not been established with these regimens. **5.16 Increased Toxicity in Developing Organs:** The safety and effectiveness of VOTRIENT in pediatric patients have not been established. VOTRIENT is not indicated for use in pediatric patients. Based on its mechanism of action, pazopanib may have severe effects on organ growth and maturation during early post-natal development. Administration of pazopanib to juvenile rats less than 21 days old resulted in toxicity to the lungs, liver, heart, and kidney and in death at doses significantly lower than the clinically recommended dose or doses tolerated in older animals. VOTRIENT may potentially cause serious adverse effects on organ development in pediatric patients, particularly in patients younger than 2 years of age *[see Use in Specific Populations (8.4)]*. **5.17 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. Potentially serious adverse reactions with VOTRIENT included hepatotoxicity, QT prolongation and torsades de pointes, cardiac dysfunction, hemorrhagic events, arterial and venous thromboembolic events, thrombotic microangiopathy, gastrointestinal perforation and fistula, Reversible Posterior Leukoencephalopathy Syndrome (RPLS), hypertension, infection, and increased toxicity with other cancer therapies *[see Warnings and Precautions (5.1-5.10, 5.14-5.15)]*. Renal Cell Carcinoma: The safety of VOTRIENT has been evaluated in 977 patients in the monotherapy trials which included 586 patients with RCC at the time of NDA submission. 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 trial *[see Clinical Studies (14.1) 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 of patients on VOTRIENT required a dose interruption. Thirty-six percent of patients on VOTRIENT were dose reduced. Table 1 presents the most common adverse reactions occurring in ≥10% of patients who received VOTRIENT.

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

	VOTRIENT (N=290)			Placebo (N=145)		
	All Grades[a]	Grade 3	Grade 4	All Grades[a]	Grade 3	Grade 4
Adverse Reactions	%	%	%	%	%	%
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%), dysphonia (4% 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%).

Additional adverse reactions from other clinical trials in RCC patients treated with VOTRIENT are listed below:
Musculoskeletal and Connective Tissue Disorders: Arthralgia, muscle spasms.

Table 2 presents the most common laboratory abnormalities occurring in >10% of patients who received VOTRIENT and more commonly (≥5%) in patients who received VOTRIENT versus placebo.

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

	VOTRIENT (N=290)			Placebo (N=145)		
	All Grades[a]	Grade 3	Grade 4	All Grades[a]	Grade 3	Grade 4
Parameters	%	%	%	%	%	%
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.

Diarrhea: Diarrhea occurred frequently and was predominantly mild to moderate in severity in the clinical trials. 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. Lipase Elevations: In a single-arm RCC trial, increases in lipase values were observed for 27% (48/181) of patients. Elevations in lipase as an adverse reaction were reported for 4% (10/225) of patients and were Grade 3 for 6 patients and Grade 4 for 1 patient. In the RCC trials of VOTRIENT, clinical pancreatitis was observed in <1% (4/586) of patients. Pneumothorax: Two of 290 patients treated with VOTRIENT and no patient on the placebo arm in the randomized RCC trial developed a pneumothorax. Bradycardia: In the randomized trial of VOTRIENT for the treatment of RCC, bradycardia based on vital signs (<60 beats per minute) was observed in 19% (52/280) of patients treated with VOTRIENT and in 11% (16/144) of patients on the placebo arm. Bradycardia was reported as an adverse reaction in 2% (7/290) of patients treated with VOTRIENT compared to <1% (1/145) of patients treated with placebo. **6.2 Postmarketing Experience:** The following adverse reactions have been identified during post approval use of VOTRIENT. Because these reactions are reported voluntarily from a population of uncertain size it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure. Gastrointestinal Disorders: Pancreatitis

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) increases pazopanib concentrations and should be avoided. Consider an alternate concomitant medication with no or minimal potential to inhibit CYP3A4 *[see Clinical Pharmacology (12.3) of full prescribing information]*. If coadministration of a strong CYP3A4 inhibitor is warranted, reduce the dose of VOTRIENT to 400 mg *[see Dosage and Administration (2.2)]*. Grapefruit or 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. Consider an alternate concomitant medication with no or minimal enzyme induction potential. VOTRIENT should not be used if chronic use of strong CYP3A4 inducers cannot be avoided *[see Dosage and Administration (2.2)]*. **7.2 Drugs That Inhibit Transporters:** In vitro studies suggested that pazopanib is a substrate of P-glycoprotein (Pgp) and breast cancer resistance protein (BCRP). Therefore, absorption and subsequent elimination of pazopanib may be influenced by products that affect Pgp and BCRP. Concomitant treatment with strong inhibitors of Pgp or breast cancer resistance protein (BCRP) should be avoided due to risk of increased exposure to pazopanib. Selection of alternative concomitant medicinal products with no or minimal potential to inhibit Pgp or BCRP should be considered. **7.3 Effects of Pazopanib on CYP Substrates:** Results from drug-drug interaction trials 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]*. **7.4 Effect of Concomitant use of VOTRIENT and Simvastatin:** Concomitant use of VOTRIENT and simvastatin increases the incidence of ALT elevations. Across monotherapy studies with VOTRIENT, ALT >3 X ULN was reported in 126/895 (14%) of patients who did not use statins, compared with 11/41 (27%) of patients who had concomitant use of simvastatin. If a patient receiving concomitant simvastatin develops ALT elevations, follow dosing guidelines for VOTRIENT or consider alternatives to VOTRIENT *[see Warnings and Precautions (5.1)]*. Alternatively, consider discontinuing simvastatin *[see Warnings and Precautions (5.1)]*. Insufficient data are available to assess the risk of concomitant administration of alternative statins and VOTRIENT. **7.5 Drugs That Raise Gastric pH:** In a drug interaction trial in patients with solid tumors, concomitant administration of pazopanib with esomeprazole, a proton pump inhibitor (PPI), decreased the exposure of pazopanib by approximately 40% (AUC and C_{max}). Therefore, concomitant use of VOTRIENT with drugs that raise gastric pH should be avoided. If such drugs are needed, short-acting antacids should be considered in place of PPIs and H2 receptor antagonists. Separate antacid and pazopanib dosing by several hours to avoid a reduction in pazopanib exposure *[see Clinical Pharmacology (12.3) of full prescribing information]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy: Pregnancy Category D *[see Warnings and Precautions (5.17)]*. 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). 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. **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 rats, weaning occurs at day 21 postpartum which approximately equates to a human pediatric age of 2 years. In a juvenile animal toxicology study performed in rats, when animals were dosed from day 9 through day 14 postpartum (pre-weaning), pazopanib caused abnormal organ growth/maturation in the kidney, lung, liver and heart at approximately 0.1 times the clinical exposure, based on AUC in adult patients receiving VOTRIENT. At approximately 0.4 times the clinical exposure (based on the AUC in adult patients), pazopanib administration resulted in mortality. 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 and animals required dose reductions due to body weight loss and morbidity. 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 doses ≥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. Similar findings were noted in repeat-dose studies in juvenile rats dosed with pazopanib beginning day 21 postpartum (post-weaning). In the post-weaning animals, the occurrence of changes in teeth and bones occurred earlier and with greater severity than in older animals. There was evidence of tooth degeneration and decreased bone growth at doses ≥30 mg/kg (approximately 0.1 to 0.2 times the AUC in human adults at the clinically recommended dose). Pazopanib exposure in juvenile rats was lower than that seen at the same dose levels in adult animals, based on comparative AUC values. At pazopanib doses approximately 0.5 to 0.7 times the exposure in adult patients at the clinically recommended dose, decreased bone growth in juvenile rats persisted even after the end of the dosing period. Finally, despite lower pazopanib exposures than those reported in adult animals or adult humans, juvenile animals administered 300 mg/kg/dose pazopanib required dose reduction within 4 weeks of dosing initiation due to significant toxicity, although adult animals could tolerate this same dose for at least 3 times as long *[see Warnings and Precautions (5.16)]*. **8.5 Geriatric Use:** In clinical trials with VOTRIENT for the treatment of RCC, 33% (196/582) of patients were aged ≥65 years. No overall differences in safety or effectiveness of VOTRIENT were observed between these patients and younger patients. 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:** 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 analysis of data from a pharmacokinetic study of pazopanib in patients with varying degrees of hepatic dysfunction suggested that no dose adjustment is required in patients with mild hepatic impairment [either total bilirubin within normal limit (WNL) with ALT > ULN or bilirubin >1 X to 1.5 X ULN regardless of the ALT value]. The maximum tolerated dose in patients with moderate hepatic impairment (total bilirubin >1.5 X to 3 X ULN regardless of the ALT value) was 200 mg per day (N=11). The median steady-state C_{max} and $AUC_{(0-24)}$ achieved at this dose was approximately 40% and 29%, respectively, of that seen in patients with normal hepatic function at the recommended daily dose of 800 mg. The maximum dose explored in patients with severe hepatic impairment (total bilirubin >3 X ULN regardless of the ALT value) was 200 mg per day (N=14). This dose was not well tolerated. Median exposures achieved at this dose were approximately 18% and 15% of those seen in patients with normal liver function at the recommended daily dose of 800 mg. Therefore, VOTRIENT is not recommended in these patients *[see Clinical Pharmacology (12.3) of full prescribing information]*. **8.7 Renal Impairment:** Patients with renal cell cancer and mild/moderate renal impairment (creatinine clearance ≥30 mL/min) were included in clinical trials 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 patients 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 Weeks 3, 5, 7, and 9. Thereafter, monitor at Month 3 and at Month 4, and as clinically indicated. Inform patients that they should report signs and symptoms of liver dysfunction to their healthcare provider right away.
- Prolonged QT intervals and torsades de pointes have been observed. Patients should be advised that ECG monitoring may be performed. Patients should be advised to inform their physicians of concomitant medications.
- Cardiac dysfunction (such as CHF and LVEF decrease) has been observed in patients at risk (e.g., prior anthracycline therapy) particularly in association with development or worsening of hypertension. Patients should be advised to report hypertension or signs and symptoms of congestive heart failure.
- Serious hemorrhagic events have been reported. Patients should be advised to report unusual bleeding.
- Arterial thrombotic events have been reported. Patients should be advised to report signs or symptoms of an arterial thrombosis.
- Reports of pneumothorax and venous thromboembolic events including pulmonary embolus have been reported. Patients should be advised to report if new onset of dyspnea, chest pain, or localized limb edema occurs.
- Advise patients to inform their doctor if they have worsening of neurological function consistent with RPLS (headache, seizure, lethargy, confusion, blindness, and other visual and neurologic disturbances).
- Hypertension and hypertensive crisis have been reported. Patients should be advised to monitor blood pressure early in the course of therapy and frequently thereafter and report increases of blood pressure or symptoms such as blurred vision, confusion, severe headache, or nausea and vomiting.
- GI perforation or fistula has occurred. Advise patients to report signs and symptoms of a GI perforation or fistula.
- VEGFR inhibitors such as VOTRIENT may impair wound healing. Advise patients to stop VOTRIENT at least 7 days prior to a scheduled surgery.
- Hypothyroidism and proteinuria have been reported. Advise patients that thyroid function testing and urinalysis will be performed during treatment.
- Serious infections including some with fatal outcomes have been reported. Advise patients to promptly report any signs or symptoms of infection.
- Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant.
- 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.
- 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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Revised: 06/2014
VTR:12BRS

Printed in USA. 49716R0 June 2014

Kidney Cancer
JOURNAL

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