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# Kidney Cancer JOURNAL

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## Genetic Testing and Management in Early-Onset Kidney Cancer

## Sunitinib Treatment Paradigm Shifting to Alternate Dosing Schedule

## Renal Mass Biopsy: Routine Use Could Optimize Treatment Decisions




**2014 ASCO: Take-Home Messages**

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


## 6.7 months median PFS with INLYTA vs 4.7 months with sorafenib

INLYTA is indicated for the treatment of advanced renal cell carcinoma (RCC) after failure of one prior systemic therapy.

**Important Safety Information**

**Hypertension** including hypertensive crisis has been observed. Blood pressure should be well controlled prior to initiating INLYTA. Monitor for hypertension and treat as needed. For persistent hypertension, despite use of antihypertensive medications, reduce the dose. Discontinue INLYTA if hypertension is severe and persistent despite use of antihypertensive therapy and dose reduction of INLYTA, and discontinuation should be considered if there is evidence of hypertensive crisis.

**Arterial and venous thrombotic events** have been observed and can be fatal. Use with caution in patients who are at increased risk or who have a history of these events.

**Hemorrhagic events**, including fatal events, have been reported. INLYTA has not been studied in patients with evidence of untreated brain metastasis or recent active gastrointestinal bleeding and should not be used in those patients. If any bleeding requires medical intervention, temporarily interrupt the INLYTA dose.

**Gastrointestinal perforation and fistula**, including death, have occurred. Use with caution in patients at risk for gastrointestinal perforation or fistula. Monitor for symptoms of gastrointestinal perforation or fistula periodically throughout treatment.

**Hypothyroidism** requiring thyroid hormone replacement has been reported. Monitor thyroid function before initiation of, and periodically throughout, treatment.

No formal studies of the effect of INLYTA on **wound healing** have been conducted. Stop INLYTA at least 24 hours prior to scheduled surgery.

**Reversible Posterior Leukoencephalopathy Syndrome (RPLS)** has been observed. If signs or symptoms occur, permanently discontinue treatment.

Monitor for **proteinuria** before initiation of, and periodically throughout, treatment. For moderate to severe proteinuria, reduce the dose or temporarily interrupt treatment.

Inlyta®
axitinib 1mg and 5mg tablets

*for the treatment of advanced RCC after failure of one prior systemic therapy*

*What truly matters to you in 2nd-line mRCC?*

# EVIDENCE

*In the phase 3, head-to-head study of exclusively 2nd-line patients with mRCC...*

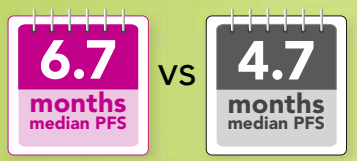
**INLYTA was the 1st agent to demonstrate**

## SUPERIOR EFFICACY

**to sorafenib**

Primary endpoint: PFS

HR=0.67 (95% CI: 0.54, 0.81; *P*<.0001)




**INLYTA** (n=361) **sorafenib** (n=362)

95% CI: 6.3, 8.6 and 4.6, 5.6, respectively

Data are from a multicenter, open-label, phase 3 trial of 723 patients with mRCC after failure of 1st-line therapy (sunitinib-, temsirolimus-, bevacizumab-, or cytokine-containing regimen). Patients were randomized to either INLYTA (5 mg twice daily) or sorafenib (400 mg twice daily) with dose adjustments allowed in both groups. Primary endpoint was PFS. Secondary endpoints included ORR, OS, and safety and tolerability.[1,2]

**Liver enzyme elevation** has been observed during treatment with INLYTA. Monitor ALT, AST, and bilirubin before initiation of, and periodically throughout, treatment.

For patients with moderate **hepatic impairment**, the starting dose should be decreased. INLYTA has not been studied in patients with severe hepatic impairment.

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

Avoid strong **CYP3A4/5 inhibitors**. If unavoidable, reduce the dose. Grapefruit or grapefruit juice may also increase INLYTA plasma concentrations and should be avoided.

Avoid strong **CYP3A4/5 inducers** and, if possible, avoid moderate CYP3A4/5 inducers.

The most common (≥20%) **adverse events (AEs)** occurring in patients receiving INLYTA (all grades, vs sorafenib) were diarrhea, hypertension, fatigue, decreased appetite, nausea, dysphonia, hand-foot syndrome, weight decreased, vomiting, asthenia, and constipation.

The most common (≥10%) **grade 3/4 AEs** occurring in patients receiving INLYTA (vs sorafenib) were hypertension, diarrhea, and fatigue.

The most common (≥20%) **lab abnormalities** occurring in patients receiving INLYTA (all grades, vs sorafenib) included increased creatinine, decreased bicarbonate, hypocalcemia, decreased hemoglobin, decreased lymphocytes (absolute), increased ALP, hyperglycemia, increased lipase, increased amylase, increased ALT, and increased AST.

*Please see brief summary on the following pages.*

Inlyta®
axitinib 1mg and 5mg tablets

**INLYTA®** (AXITINIB) TABLETS FOR ORAL ADMINISTRATION

Initial U.S. Approval: 2012

**Brief Summary of Prescribing Information**

**INDICATIONS AND USAGE:** INLYTA is indicated for the treatment of advanced renal cell carcinoma (RCC) after failure of one prior systemic therapy.

**DOSAGE AND ADMINISTRATION**

**Recommended Dosing.** The recommended starting oral dose of INLYTA is 5 mg twice daily. Administer INLYTA doses approximately 12 hours apart with or without food. INLYTA should be swallowed whole with a glass of water.

If the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time.

**Dose Modification Guidelines.** Dose increase or reduction is recommended based on individual safety and tolerability.

Over the course of treatment, patients who tolerate INLYTA for at least two consecutive weeks with no adverse reactions >Grade 2 (according to the Common Toxicity Criteria for Adverse Events [CTCAE]), are normotensive, and are not receiving anti-hypertension medication, may have their dose increased. When a dose increase from 5 mg twice daily is recommended, the INLYTA dose may be increased to 7 mg twice daily, and further to 10 mg twice daily using the same criteria.

Over the course of treatment, management of some adverse drug reactions may require temporary interruption or permanent discontinuation and/or dose reduction of INLYTA therapy *[see Warnings and Precautions]*. If dose reduction from 5 mg twice daily is required, the recommended dose is 3 mg twice daily. If additional dose reduction is required, the recommended dose is 2 mg twice daily.

Strong CYP3A4/5 Inhibitors: The concomitant use of strong CYP3A4/5 inhibitors should be avoided (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole). Selection of an alternate concomitant medication with no or minimal CYP3A4/5 inhibition potential is recommended. Although INLYTA dose adjustment has not been studied in patients receiving strong CYP3A4/5 inhibitors, if a strong CYP3A4/5 inhibitor must be co-administered, a dose decrease of INLYTA by approximately half is recommended, as this dose reduction is predicted to adjust the axitinib area under the plasma concentration vs time curve (AUC) to the range observed without inhibitors. The subsequent doses can be increased or decreased based on individual safety and tolerability. If co-administration of the strong inhibitor is discontinued, the INLYTA dose should be returned (after 3–5 half-lives of the inhibitor) to that used prior to initiation of the strong CYP3A4/5 inhibitor.

Hepatic Impairment: No starting dose adjustment is required when administering INLYTA to patients with mild hepatic impairment (Child-Pugh class A). Based on the pharmacokinetic data, the INLYTA starting dose should be reduced by approximately half in patients with baseline moderate hepatic impairment (Child-Pugh class B). The subsequent doses can be increased or decreased based on individual safety and tolerability. INLYTA has not been studied in patients with severe hepatic impairment (Child-Pugh class C).

**DOSAGE FORMS AND STRENGTHS**

1 mg tablets of INLYTA: red, film-coated, oval tablets, debossed with "Pfizer" on one side and "1 XNB" on the other side.

5 mg tablets of INLYTA: red, film-coated, triangular tablets, debossed with "Pfizer" on one side and "5 XNB" on the other side.

**CONTRAINDICATIONS:** None

**WARNINGS AND PRECAUTIONS**

**Hypertension and Hypertensive Crisis.** In a controlled clinical study with INLYTA for the treatment of patients with RCC, hypertension was reported in 145/359 patients (40%) receiving INLYTA and 103/355 patients (29%) receiving sorafenib. Grade 3/4 hypertension was observed in 56/359 patients (16%) receiving INLYTA and 39/355 patients (11%) receiving sorafenib. Hypertensive crisis was reported in 2/359 patients (<1%) receiving INLYTA and none of the patients receiving sorafenib. The median onset time for hypertension (systolic blood pressure >150 mmHg or diastolic blood pressure >100 mmHg) was within the first month of the start of INLYTA treatment and blood pressure increases have been observed as early as 4 days after starting INLYTA. Hypertension was managed with standard antihypertensive therapy. Discontinuation of INLYTA treatment due to hypertension occurred in 1/359 patients (<1%) receiving INLYTA and none of the patients receiving sorafenib.

Blood pressure should be well-controlled prior to initiating INLYTA. Patients should be monitored for hypertension and treated as needed with standard anti-hypertensive therapy. In the case of persistent hypertension despite use of anti-hypertensive medications, reduce the INLYTA dose. Discontinue INLYTA if hypertension is severe and persistent despite anti-hypertensive therapy and dose reduction of INLYTA, and discontinuation should be considered if there is evidence of hypertensive crisis. If INLYTA is interrupted, patients receiving antihypertensive medications should be monitored for hypotension.

**Arterial Thromboembolic Events.** In clinical trials, arterial thromboembolic events have been reported, including deaths. In a controlled clinical study with INLYTA for the treatment of patients with RCC, Grade 3/4 arterial thromboembolic events were reported in 4/359 patients (1%) receiving INLYTA and 4/355 patients (1%) receiving sorafenib. Fatal cerebrovascular accident was reported in 1/359 patients (<1%) receiving INLYTA and none of the patients receiving sorafenib *[see Adverse Reactions]*.

In clinical trials with INLYTA, arterial thromboembolic events (including transient ischemic attack, cerebrovascular accident, myocardial infarction, and retinal artery occlusion) were reported in 17/715 patients (2%), with two deaths secondary to cerebrovascular accident.

Use INLYTA with caution in patients who are at risk for, or who have a history of, these events. INLYTA has not been studied in patients who had an arterial thromboembolic event within the previous 12 months.

**Venous Thromboembolic Events.** In clinical trials, venous thromboembolic events have been reported, including deaths. In a controlled clinical study with INLYTA for the treatment of patients with RCC, venous thromboembolic events were reported in 11/359 patients (3%) receiving INLYTA and 2/355 patients (1%) receiving sorafenib. Grade 3/4 venous thromboembolic events were reported in 9/359 patients (3%) receiving INLYTA (including pulmonary embolism, deep vein thrombosis, retinal vein occlusion and retinal vein thrombosis) and 2/355 patients (1%) receiving sorafenib. Fatal pulmonary embolism was reported in 1/359 patients (<1%) receiving INLYTA and none of the patients receiving sorafenib. In clinical trials with INLYTA, venous thromboembolic events were reported in 22/715 patients (3%), with two deaths secondary to pulmonary embolism.

Use INLYTA with caution in patients who are at risk for, or who have a history of, these events. INLYTA has not been studied in patients who had a venous thromboembolic event within the previous 6 months.

**Hemorrhage.** In a controlled clinical study with INLYTA for the treatment of patients with RCC, hemorrhagic events were reported in 58/359 patients (16%) receiving INLYTA and 64/355 patients (18%) receiving sorafenib. Grade 3/4 hemorrhagic events were reported in 5/359 (1%) patients receiving INLYTA (including cerebral hemorrhage, hematuria, hemoptysis, lower gastrointestinal hemorrhage, and melena) and 11/355 (3%) patients receiving sorafenib. Fatal hemorrhage was reported in 1/359 patients (<1%) receiving INLYTA (gastric hemorrhage) and 3/355 patients (1%) receiving sorafenib.

INLYTA has not been studied in patients who have evidence of untreated brain metastasis or recent active gastrointestinal bleeding and should not be used in those patients. If any bleeding requires medical intervention, temporarily interrupt the INLYTA dose.

**Gastrointestinal Perforation and Fistula Formation.** In a controlled clinical study with INLYTA for the treatment of patients with RCC, gastrointestinal perforation was reported in 1/359 patients (<1%) receiving INLYTA and none of the patients receiving sorafenib. In clinical trials with INLYTA, gastrointestinal perforation was reported in 5/715 patients (1%), including one death. In addition to cases of gastrointestinal perforation, fistulas were reported in 4/715 patients (1%).

Monitor for symptoms of gastrointestinal perforation or fistula periodically throughout treatment with INLYTA.

**Thyroid Dysfunction.** In a controlled clinical study with INLYTA for the treatment of patients with RCC, hypothyroidism was reported in 69/359 patients (19%) receiving INLYTA and 29/355 patients (8%) receiving sorafenib. Hyperthyroidism was reported in 4/359 patients (1%) receiving INLYTA and 4/355 patients (1%) receiving sorafenib. In patients who had thyroid stimulating hormone (TSH) <5 µU/mL before treatment, elevations of TSH to ≥10 µU/mL occurred in 79/245 patients (32%) receiving INLYTA and 25/232 patients (11%) receiving sorafenib.

Monitor thyroid function before initiation of, and periodically throughout, treatment with INLYTA. Treat hypothyroidism and hyperthyroidism according to standard medical practice to maintain euthyroid state.

**Wound Healing Complications.** No formal studies of the effect of INLYTA on wound healing have been conducted.

Stop treatment with INLYTA at least 24 hours prior to scheduled surgery. The decision to resume INLYTA therapy after surgery should be based on clinical judgment of adequate wound healing.

**Reversible Posterior Leukoencephalopathy Syndrome.** In a controlled clinical study with INLYTA for the treatment of patients with RCC, reversible posterior leukoencephalopathy syndrome (RPLS) was reported in 1/359 patients (<1%) receiving INLYTA and none of the patients receiving sorafenib. There were two additional reports of RPLS in other clinical trials with INLYTA.

RPLS is a neurological disorder which can present with headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging is necessary to confirm the diagnosis of RPLS. Discontinue INLYTA in patients developing RPLS. The safety of reinitiating INLYTA therapy in patients previously experiencing RPLS is not known.

**Proteinuria.** In a controlled clinical study with INLYTA for the treatment of patients with RCC, proteinuria was reported in 39/359 patients (11%) receiving INLYTA and 26/355 patients (7%) receiving sorafenib. Grade 3 proteinuria was reported in 11/359 patients (3%) receiving INLYTA and 6/355 patients (2%) receiving sorafenib.

Monitoring for proteinuria before initiation of, and periodically throughout, treatment with INLYTA is recommended. For patients who develop moderate to severe proteinuria, reduce the dose or temporarily interrupt INLYTA treatment.

**Elevation of Liver Enzymes.** In a controlled clinical study with INLYTA for the treatment of patients with RCC, alanine aminotransferase (ALT) elevations of all grades occurred in 22% of patients on both arms, with Grade 3/4 events in <1% of patients on the INLYTA arm and 2% of patients on the sorafenib arm.

Monitor ALT, aspartate aminotransferase (AST) and bilirubin before initiation of and periodically throughout treatment with INLYTA.

**Hepatic Impairment.** The systemic exposure to axitinib was higher in subjects with moderate hepatic impairment (Child-Pugh class B) compared to subjects with normal hepatic function. A dose decrease is recommended when administering INLYTA to patients with moderate hepatic impairment (Child-Pugh class B). INLYTA has not been studied in patients with severe hepatic impairment (Child-Pugh class C).

**Pregnancy.** INLYTA can cause fetal harm when administered to a pregnant woman based on its mechanism of action. There are no adequate and well-controlled studies in pregnant women using INLYTA. In developmental toxicity studies in mice, axitinib was teratogenic, embryotoxic and fetotoxic at maternal exposures that were lower than human exposures at the recommended clinical dose.

Women of childbearing potential should be advised to avoid becoming pregnant while receiving INLYTA. If this drug is used during pregnancy, or if a patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus.

**ADVERSE REACTIONS**

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

The safety of INLYTA has been evaluated in 715 patients in monotherapy studies, which included 537 patients with advanced RCC. The data described reflect exposure to INLYTA in 359 patients with advanced RCC who participated in a randomized clinical study versus sorafenib.

The following risks, including appropriate action to be taken, are discussed in greater detail in other sections of the label: hypertension, arterial thromboembolic events, venous thromboembolic events, hemorrhage, gastrointestinal perforation and fistula formation, thyroid dysfunction, wound healing complications, RPLS, proteinuria, elevation of liver enzymes, and fetal development.

**Clinical Trials Experience.** The median duration of treatment was 6.4 months (range 0.03 to 22.0) for patients who received INLYTA and 5.0 months (range 0.03 to 20.1) for patients who received sorafenib. Dose modifications or temporary delay of treatment due to an adverse reaction occurred in 199/359 patients (55%) receiving INLYTA and 220/355 patients (62%) receiving sorafenib. Permanent discontinuation due to an adverse reaction occurred in 34/359 patients (9%) receiving INLYTA and 46/355 patients (13%) receiving sorafenib.

The most common (≥20%) adverse reactions observed following treatment with INLYTA were diarrhea, hypertension, fatigue, decreased appetite, nausea, dysphonia, palmar-plantar erythrodysesthesia (hand-foot) syndrome, weight decreased, vomiting, asthenia, and constipation.

The following table presents adverse reactions reported in ≥10% patients who received INLYTA or sorafenib.

**Adverse Reactions Occurring in ≥10% of Patients Who Received INLYTA or Sorafenib**

| Adverse Reaction[a] | INLYTA (N=359) | | Sorafenib (N=355) | |
|---|---|---|---|---|
| | All Grades[b] | Grade 3/4 | All Grades[b] | Grade 3/4 |
| | % | % | % | % |
| Diarrhea | 55 | 11 | 53 | 7 |
| Hypertension | 40 | 16 | 29 | 11 |
| Fatigue | 39 | 11 | 32 | 5 |
| Decreased appetite | 34 | 5 | 29 | 4 |
| Nausea | 32 | 3 | 22 | 1 |
| Dysphonia | 31 | 0 | 14 | 0 |
| Palmar-plantar erythrodysesthesia syndrome | 27 | 5 | 51 | 16 |
| Weight decreased | 25 | 2 | 21 | 1 |
| Vomiting | 24 | 3 | 17 | 1 |
| Asthenia | 21 | 5 | 14 | 3 |
| Constipation | 20 | 1 | 20 | 1 |
| Hypothyroidism | 19 | <1 | 8 | 0 |
| Cough | 15 | 1 | 17 | 1 |
| Mucosal inflammation | 15 | 1 | 12 | 1 |
| Arthralgia | 15 | 2 | 11 | 1 |
| Stomatitis | 15 | 1 | 12 | <1 |
| Dyspnea | 15 | 3 | 12 | 3 |
| Abdominal pain | 14 | 2 | 11 | 1 |
| Headache | 14 | 1 | 11 | 0 |
| Pain in extremity | 13 | 1 | 14 | 1 |
| Rash | 13 | <1 | 32 | 4 |
| Proteinuria | 11 | 3 | 7 | 2 |
| Dysgeusia | 11 | 0 | 8 | 0 |
| Dry skin | 10 | 0 | 11 | 0 |
| Dyspepsia | 10 | 0 | 2 | 0 |
| Pruritus | 7 | 0 | 12 | 0 |
| Alopecia | 4 | 0 | 32 | 0 |
| Erythema | 2 | 0 | 10 | <1 |

[a]Percentages are treatment-emergent, all-causality events

[b]National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0

Selected adverse reactions (all grades) that were reported in <10% of patients treated with INLYTA included dizziness (9%), upper abdominal pain (8%), myalgia (7%), dehydration (6%), epistaxis (6%), anemia (4%), hemorrhoids (4%), hematuria (3%), tinnitus (3%), lipase increased (3%), glossodynia (3%), pulmonary embolism (2%), rectal hemorrhage (2%), hemoptysis (2%), deep vein thrombosis (1%), retinal-vein occlusion/thrombosis (1%), polycythemia (1%), and transient ischemic attack (1%).

The following table presents the most common laboratory abnormalities reported in ≥10% patients who received INLYTA or sorafenib.

**Laboratory Abnormalities Occurring in ≥10% of Patients Who Received INLYTA or Sorafenib**

| Laboratory Abnormality | N | INLYTA | | N | Sorafenib | |
|---|---|---|---|---|---|---|
| | | All Grades[a] | Grade 3/4 | | All Grades[a] | Grade 3/4 |
| | | % | % | | % | % |
| **Hematology** | | | | | | |
| Hemoglobin decreased | 320 | 35 | <1 | 316 | 52 | 4 |
| Lymphocytes (absolute) decreased | 317 | 33 | 3 | 309 | 36 | 4 |
| Platelets decreased | 312 | 15 | <1 | 310 | 14 | 0 |
| White blood cells decreased | 320 | 11 | 0 | 315 | 16 | <1 |
| **Chemistry** | | | | | | |
| Creatinine increased | 336 | 55 | 0 | 318 | 41 | <1 |
| Bicarbonate decreased | 314 | 44 | <1 | 291 | 43 | 0 |
| Hypocalcemia | 336 | 39 | 1 | 319 | 59 | 2 |
| ALP increased | 336 | 30 | 1 | 319 | 34 | 1 |
| Hyperglycemia | 336 | 28 | 2 | 319 | 23 | 2 |
| Lipase increased | 338 | 27 | 5 | 319 | 46 | 15 |
| Amylase increased | 338 | 25 | 2 | 319 | 33 | 2 |
| ALT increased | 331 | 22 | <1 | 313 | 22 | 2 |
| AST increased | 331 | 20 | <1 | 311 | 25 | 1 |
| Hypernatremia | 338 | 17 | 1 | 319 | 13 | 1 |
| Hypoalbuminemia | 337 | 15 | <1 | 319 | 18 | 1 |
| Hyperkalemia | 333 | 15 | 3 | 314 | 10 | 3 |
| Hypoglycemia | 336 | 11 | <1 | 319 | 8 | <1 |
| Hyponatremia | 338 | 13 | 4 | 319 | 11 | 2 |
| Hypophosphatemia | 336 | 13 | 2 | 318 | 49 | 16 |

[a]National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase

Selected laboratory abnormalities (all grades) that were reported in <10% of patients treated with INLYTA included hemoglobin increased (above the upper limit of normal) (9% for INLYTA versus 1% for sorafenib) and hypercalcemia (6% for INLYTA versus 2% for sorafenib).

**DRUG INTERACTIONS**

*In vitro* data indicate that axitinib is metabolized primarily by CYP3A4/5 and, to a lesser extent, CYP1A2, CYP2C19, and uridine diphosphate-glucuronosyltransferase (UGT) 1A1.

**CYP3A4/5 Inhibitors.** Co-administration of ketoconazole, a strong inhibitor of CYP3A4/5, increased the plasma exposure of axitinib in healthy volunteers. Co-administration of INLYTA with strong CYP3A4/5 inhibitors should be avoided. Grapefruit or grapefruit juice may also increase axitinib plasma concentrations and should be avoided. Selection of concomitant medication with no or minimal CYP3A4/5 inhibition potential is recommended. If a strong CYP3A4/5 inhibitor must be coadministered, the INLYTA dose should be reduced *[see Dosage and Administration]*.

**CYP3A4/5 Inducers.** Co-administration of rifampin, a strong inducer of CYP3A4/5, reduced the plasma exposure of axitinib in healthy volunteers. Co-administration of INLYTA with strong CYP3A4/5 inducers (e.g., rifampin, dexamethasone, phenytoin, carbamazepine, rifabutin, rifapentin, phenobarbital, and St. John's wort) should be avoided. Selection of concomitant medication with no or minimal CYP3A4/5 induction potential is recommended *[see Dosage and Administration]*. Moderate CYP3A4/5 inducers (e.g., bosentan, efavirenz, etravirine, modafinil, and nafcillin) may also reduce the plasma exposure of axitinib and should be avoided if possible.

**USE IN SPECIFIC POPULATIONS**

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

There are no adequate and well-controlled studies with INLYTA in pregnant women. INLYTA can cause fetal harm when administered to a pregnant woman based on its mechanism of action. Axitinib was teratogenic, embryotoxic and fetotoxic in mice at exposures lower than human exposures at the recommended starting dose. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus.

Oral axitinib administered twice daily to female mice prior to mating and through the first week of pregnancy caused an increase in post-implantation loss at all doses tested (≥15 mg/kg/dose, approximately 10 times the systemic exposure (AUC) in patients at the recommended starting dose). In an embryo-fetal developmental toxicity study, pregnant mice received oral doses of 0.15, 0.5 and 1.5 mg/kg/dose axitinib twice daily during the period of organogenesis. Embryo-fetal toxicities observed in the absence of maternal toxicity included malformation (cleft palate) at 1.5 mg/kg/dose (approximately 0.5 times the AUC in patients at the recommended starting dose) and variation in skeletal ossification at ≥0.5 mg/kg/dose (approximately 0.15 times the AUC in patients at the recommended starting dose).

**Nursing Mothers.** It is not known whether axitinib is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from INLYTA, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**Pediatric Use.** The safety and efficacy of INLYTA in pediatric patients have not been studied.

Toxicities in bone and teeth were observed in immature mice and dogs administered oral axitinib twice daily for 1 month or longer. Effects in bone consisted of thickened growth plates in mice and dogs at ≥15 mg/kg/dose (approximately 6 and 15 times, respectively, the systemic exposure (AUC) in patients at the recommended starting dose). Abnormalities in growing incisor teeth (including dental caries, malocclusions and broken and/or missing teeth) were observed in mice administered oral axitinib twice daily at ≥5 mg/kg/dose (approximately 1.5 times the AUC in patients at the recommended starting dose). Other toxicities of potential concern to pediatric patients have not been evaluated in juvenile animals.

**Geriatric Use.** In a controlled clinical study with INLYTA for the treatment of patients with RCC, 123/359 patients (34%) treated with INLYTA were ≥65 years of age. Although greater sensitivity in some older individuals cannot be ruled out, no overall differences were observed in the safety and effectiveness of INLYTA between patients who were ≥65 years of age and younger.

No dosage adjustment is required in elderly patients.

**Hepatic Impairment.** In a dedicated hepatic impairment trial, compared to subjects with normal hepatic function, systemic exposure following a single dose of INLYTA was similar in subjects with baseline mild hepatic impairment (Child-Pugh class A) and higher in subjects with baseline moderate hepatic impairment (Child-Pugh class B).

No starting dose adjustment is required when administering INLYTA to patients with mild hepatic impairment (Child-Pugh class A). A starting dose decrease is recommended when administering INLYTA to patients with moderate hepatic impairment (Child-Pugh class B).

INLYTA has not been studied in subjects with severe hepatic impairment (Child-Pugh class C).

**Renal Impairment.** No dedicated renal impairment trial for axitinib has been conducted. Based on the population pharmacokinetic analyses, no significant difference in axitinib clearance was observed in patients with pre-existing mild to severe renal impairment (15 mL/min ≤creatinine clearance [CLcr] <89 mL/min). No starting dose adjustment is needed for patients with pre-existing mild to severe renal impairment. Caution should be used in patients with end-stage renal disease (CLcr <15 mL/min).

**OVERDOSAGE**

There is no specific treatment for INLYTA overdose.

In a controlled clinical study with INLYTA for the treatment of patients with RCC, 1 patient inadvertently received a dose of 20 mg twice daily for 4 days and experienced dizziness (Grade 1).

In a clinical dose finding study with INLYTA, subjects who received starting doses of 10 mg twice daily or 20 mg twice daily experienced adverse reactions which included hypertension, seizures associated with hypertension, and fatal hemoptysis.

In cases of suspected overdose, INLYTA should be withheld and supportive care instituted.

**NONCLINICAL TOXICOLOGY**

**Carcinogenesis, Mutagenesis, Impairment of Fertility.** Carcinogenicity studies have not been conducted with axitinib.

Axitinib was not mutagenic in an *in vitro* bacterial reverse mutation (Ames) assay and was not clastogenic in the *in vitro* human lymphocyte chromosome aberration assay. Axitinib was genotoxic in the *in vivo* mouse bone marrow micronucleus assay.

INLYTA has the potential to impair reproductive function and fertility in humans. In repeat-dose toxicology studies, findings in the male reproductive tract were observed in the testes/epididymis (decreased organ weight, atrophy or degeneration, decreased numbers of germinal cells, hypospermia or abnormal sperm forms, reduced sperm density and count) at ≥15 mg/kg/dose administered orally twice daily in mice (approximately 7 times the systemic exposure (AUC) in patients at the recommended starting dose) and ≥1.5 mg/kg/dose administered orally twice daily in dogs (approximately 0.1 times the AUC in patients at the recommended starting dose). Findings in the female reproductive tract in mice and dogs included signs of delayed sexual maturity, reduced or absent corpora lutea, decreased uterine weights and uterine atrophy at ≥5 mg/kg/dose (approximately 1.5 or 0.3 times the AUC in patients at the recommended starting dose compared to mice and dogs, respectively).

In a fertility study in mice, axitinib did not affect mating or fertility rate when administered orally twice daily to males at any dose tested up to 50 mg/kg/dose following at least 70 days of administration (approximately 57 times the AUC in patients at the recommended starting dose). In female mice, reduced fertility and embryonic viability were observed at all doses tested (≥15 mg/kg/dose administered orally twice daily) following at least 15 days of treatment with axitinib (approximately 10 times the AUC in patients at the recommended starting dose).

**PATIENT COUNSELING INFORMATION**

**Reversible Posterior Leukoencephalopathy Syndrome.** Advise patients to inform their doctor if they have worsening of neurological function consistent with RPLS (headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances).

**Pregnancy.** Advise patients that INLYTA may cause birth defects or fetal loss and that they should not become pregnant during treatment with INLYTA. Both male and female patients should be counseled to use effective birth control during treatment with INLYTA. Female patients should also be advised against breast-feeding while receiving INLYTA.

**Concomitant Medications.** Advise patients to inform their doctor of all concomitant medications, vitamins, or dietary and herbal supplements.

**Rx only**

Issued: September 2013

**References: 1.** Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. *Lancet*. 2011;378(9807):1931-1939. **2.** Data on file. Pfizer Inc, New York, NY.

mRCC=metastatic renal cell carcinoma; ORR=objective response rate; OS=overall survival; PFS=progression-free survival.

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**Editorial Mission**
The purpose of *Kidney Cancer Journal* is to serve as a comprehensive resource of information for physicians regarding advances in the diagnosis and treatment of renal cell carcinoma. Content of the journal focuses on the impact of translational research in oncology and urology and also provides a forum for cancer patient advocacy. *Kidney Cancer Journal* is circulated to medical oncologists, hematologist-oncologists, and urologists.

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**About the Cover**
Graph depicts distribution of median and mean ages at diagnosis of renal cell carcinoma (RCC) among patients with hereditary forms of RCC using data compiled from the Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute. (Adapted from Shuch B et al, *J Clin Oncol*. 2014; 32:431-437.) Inset images copyright © Science Source.

KCJ TABLE OF CONTENTS



KCJ GUEST EDITOR'S MEMO

# Reality Check on ASCO 2014: How Many More Dots Were Connected in the Treatment of RCC?


Jose A. Karam, MD

Glimmers of new treatment approaches, tantalizing clues as to what may be on the horizon to expand the spectrum of options in immunotherapy, including checkpoint inhibitors, and emerging results from the ESPN trial represent just a small snapshot of this year's 2014 meeting of the American Society of Clinical Oncology (ASCO). *Kidney Cancer Journal* assembled a panel of experts to quickly offer their impressions of what was significant at the Scientific Sessions this year, and their encapsulating and concise observations provide some insightful comments as a postscript to the meeting (page 42).

Once again, judging from the preponderance of evidence submitted in their comments, immunotherapy seemed to be the pace setter—a theme repeated from last year. In one scientific session at ASCO on checkpoint inhibitors, we obtained more in-depth information on the antibody inhibitors of CTLA-4, PD-1, and PD-L1. These agents may mount a challenge to acceptable first-line therapies but that remains to be prospectively proven in future larger trials. The level of interest in the potential of inhibiting these immune pathways guarantees that subsequent sessions of ASCO will be highly attended to see whether concerns about toxicity can be resolved and whether a checkpoint inhibitor could be inserted into the treatment algorithm, either alone or in combination, at least in second line setting.

I urge you to examine the comments from our panel and judge for yourself what course management is likely to take as these new modalities possibly become available over the next few years. All of these directions will be explored in greater depth in the next issue of the journal as a key investigator examines the implications of a broad range of data presented in various sessions.

But if you are looking now for more in-depth analysis on RCC topics, then the three articles in this issue would merit your attention. They include:

- A report by Brian Shuch, MD, on early-onset renal cell carcinoma and the evolution in thinking on germline mutational testing in this subset of patients.
- A review by Eric Jonasch, MD, delineating how scheduling of sunitinib-moving from the traditional 4 weeks on 2 weeks off to 2 weeks on 1 week off-is changing our perception of how the use of this agent may be more

*(continued on page 64)*

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# *Kidney Cancer Journal* Author Guidelines

### Scope of Manuscripts

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

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

### Manuscript Submission

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

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### Contact information

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

### Peer Review and Editing

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

### Conflict of Interest

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

### Manuscript Preparation

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

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

### References

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

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# Essential Peer-Reviewed Reading in Kidney Cancer

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

### Cytoreductive Nephrectomy in Patients with Synchronous Metastases from Renal Cell Carcinoma: Results from the International Metastatic Renal Cell Carcinoma Database Consortium. Heng DY, Wells JC, Rini BI, et al. *Eur Urol*. 2014;June 12;[Epub ahead of print]

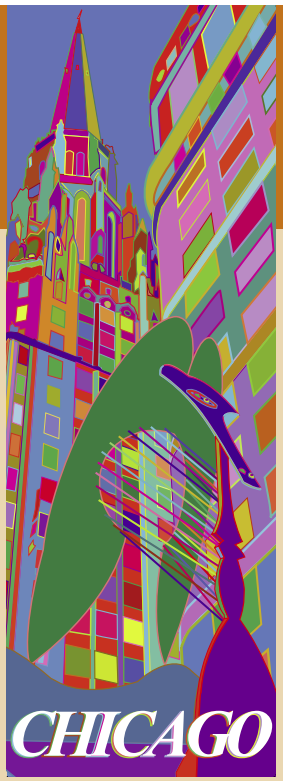
**Summary:** The benefit of cytoreductive nephrectomy (CN) for overall survival (OS) is unclear in patients with synchronous metastatic renal cell carcinoma (mRCC) in the era of targeted therapy. The objective was to determine OS benefit of CN compared with no CN in mRCC patients treated with targeted therapies. Retrospective data from patients with synchronous mRCC (n=1658) from the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) were used to compare 982 mRCC patients who had a CN with 676 mRCC patients who did not. Patients who had CN had better IMDC prognostic profiles versus those without (favorable, intermediate, or poor in 9%, 63%, and 28% vs 1%, 45%, and 54%, respectively). The median OS of patients with CN versus without CN was 20.6 versus 9.5 mo ($P$<0.0001). When adjusted for IMDC criteria to correct for imbalances, the HR of death was 0.60 (95% confidence interval, 0.52-0.69; $P$<0.0001). Patients estimated to survive <12 mo may receive marginal benefit from CN. Patients who have four or more of the IMDC prognostic criteria did not benefit from CN. Data were collected retrospectively.
**Conclusion:** CN is beneficial in synchronous mRCC patients treated with targeted therapy, even after adjusting for prognostic factors. Patients with estimated survival times <12 mo or four or more IMDC prognostic factors may not benefit from CN. This information may aid in patient selection as we await results from randomized controlled trials.

### Risk of subsequent cancers in renal cell carcinoma survivors with a family history. Chen T, Fallah M, Sundquist K, et al. *Eur J Cancer*. 2014; June 9; [Epubahead of print]

**Summary:** This study aimed at elucidating the effect of family history on the development of subsequent cancers in renal cell carcinoma (RCC) survivors and aimed at assessing whether the interactions between risks of subsequent cancers in RCC survivors and familial risk of subsequent cancer are additive or multiplicative interactions. A population-based cohort (Swedish Family-Cancer Database) of 14,267 RCC patients diagnosed in 1990-2010 was followed for cancer incidence. Standardized incidence ratios (SIRs) were calculated for subsequent cancers in RCC survivors and in RCC survivors with a family history of subsequent cancer. Familial risk of subsequent cancer was calculated for individuals with family history of specific cancer, compared to those without. For subsequent hemangioblastoma (HB) in RCC survivors, drastically elevated risk was observed for the effect of family history of HB [SIR=777 (95% confidence interval (CI): 160-2270)] and of family history of RCC [378 (46-1367)]. Colorectal, lung, prostate and RCCs favored additive interactions between risk of subsequent cancers in RCC survivors and familial risk, while endocrine glands, nervous system and urinary bladder cancers favored multiplicative interactions.
**Conclusion:** Risks of subsequent HB in RCC survivors were tremendously modified by family history of RCC or HB, which may resemble characteristics of von Hippel-Lindau syndrome and show the power of present approach to detect heritable cancer clusters. Additive or multiplicative interactions found for colorectal, lung, prostate, endocrine glands, nervous system, urinary bladder and RCCs might raise awareness among clinicians and RCC survivors with a family history of seven cancers about elevated risks of subsequent those cancers.

### Next generation sequencing of translocation renal cell carcinomas reveals novel RNA splicing partners and frequent mutations of chromatin remodeling genes. Malouf GG, Su X, Yao H, et al. *Clin Cancer Res*. 2014;June 4;[Epub ahead of print]

**Summary:** MITF/TFE translocation renal cell carcinoma (TRCC) is a rare subtype of kidney cancer. Its incidence and the genome-wide characterization of its genetic origin have not been fully elucidated. Experimental design: the authors performed RNA and exome sequencing on an exploratory set of TRCC (n=7), and validated our findings using The Cancer Genome Atlas (TCGA) clear-cell RCC (ccRCC) dataset (n=460). Results: Using the TCGA dataset, we identified 7 TRCC (1.5%) cases and determined their genomic profile. We discovered three novel partners of MITF/TFE (LUC7L3, KHSRP and KHDRBS2), which are involved in RNA splicing. TRCC displayed a unique gene expression signature as compared to other RCC types, and showed activation of MITF, the transforming growth factor 1 and the PI3K complex targets. Genes differentially spliced between TRCC and other RCC types were enriched for MITF and ID2 targets. Exome sequencing of TRCC revealed a distinct mutational spectrum as compared to ccRCC, with frequent mutations in chromatin remodeling genes (six of eight cases, three of which from the TCGA). In two cases, we identified mutations in INO80D, an ATP-dependent chromatin remodeling gene, previously shown to control the amplitude of the S phase. Knockdown of INO80D decreased cell proliferation in a novel cell line bearing LUC7L3-TFE3 translocation.
**Conclusion:** This genome-wide study defines the incidence of TRCC within a ccRCC-directed project and expands the genomic spectrum of TRCC by identifying novel MITF/TFE partners involved in RNA splicing and frequent mutations in chromatin remodeling genes. KCJ

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# ASCO 2014 at a Glance: What Are the Take-Home Messages?

*A panel of experts offer their first impressions of new findings presented at the 2014 Scientific Sessions of the American Society of Clinical Oncology with possible translational impact.*

**Brian I. Rini, MD**
*Dr Rini is a Professor of Medicine at the Cleveland Clinic Lerner College of Medicine of Case Western Reserve University in Cleveland, Ohio. A Staff member of the Department of Solid Tumor Oncology, Dr. Rini's work focuses on genitourinary malignancies.*

I think the biggest take-home message of immediate relevance to the practicing clinician from ASCO 2014 was the ESPN trial looking at either sunitinib vs everolimus in non-clear cell RCC. Although the trial was small and included many different subtypes of non-clear cell (including patients with clear cell and >20% sarcomatoid changes), there were advantages to sunitinib. Having said that, the relative activity was modest with few objective responses and a short PFS on the order of 6 months. These data reinforce my practice of a VEGFR TKI in non-clear cell patient, but also reinforce that a clinical trial is the best option for these patients and that we need to understand the biology of this heterogeneous subgroup better to come up with more effective therapeutic options.

**Nicholas J. Vogelzang, MD**
*Dr Vogelzang is a medical oncologist with Comprehensive Cancer Centers of Nevada (CCCN), Las Vegas, serves as site research leader, is the Associate Director of the Genitourinary Committee and serves on the Research Executive Committee for US Oncology Research.*

The message that I took home from ASCO 2014 is that there is considerable promise to the use of the immune check point antibody inhibitors (CTLA-4, PD-1 and PDL-1) but that they are not yet ready to displace our current 1st and 2nd line treatments. In fact, Dr Asmin reported that the combinations of pazopanib simultaneously with nivolumab and sunitinib concurrently with nivolumab had increased toxicity. Dr Hammer's presentation on nivolumab with ipilumumab as first line therapy showed good levels of activity with some long term remissions but with fairly high rates of GI toxicity. There is a plan by BMS to compare the combination to sunitinib in a phase 3 design. Meanwhile Genentech is comparing sunitinib to PDL-1 antibody to PDL-1 antibody plus avastin. In conclusion, it is certainly appropriate to refer your patients for these newer agents or clinical trials but that sunitinib and pazopanib continue to remain perfectly acceptable 1st line therapies.

**Janice P. Dutcher, MD**
*Dr Dutcher is the Immediate past-chair of ECOG Renal Cancer Subcommittee and Associate Director of the Cancer Research Foundation of New York.*

Immunotherapy and a better understanding of optimizing the anti-tumor immune response were evident in GU Oncology at ASCO 2014. Further investigations of high-dose Interleukin-2 (IL-2) derived from current Registry Data (2007-2012) indicate a major survival benefit for all IL-2-treated patients (n=97), with the median not reached for those with SD, PR or CR, and a median of 40 months for those with PD. The one-, two-

and three-year survival rates were 86%, 66% and 62% respectively (Morse et al, Abst 4523). Similar long term survival data with high dose IL-2 were presented from a single institution over a 12 year period (n=176) by Merriman etal (Abst 4577). In a small phase II study (n=21, 10 poor risk, 11 intermediate risk), long-term survival data from the combination of autologous immunotherapy (AGS-003) plus sunitinib also showed promising extension of survival compared with historical controls treated with sunitinib alone, with a median overall survival ≥ 30 months, and 33% surviving for at least 54 months. Thus durable survival is the hallmark of treatment with immunotherapy for renal cell cancer and the benchmark for new therapies that are in develop-ment. This clearly surpasses targeted therapy, but the current goal should be to extend this to greater numbers of patients.

Briefly, biomarkers were evaluated retrospectively from the CALGB trial 90206, interferon + bevacizumab vs interferon alone (Kluger et al, abst 4532). Expression of HGF was prognostic for all patients with RCC, and IL-6 was predictive of progression-free survival in bevacizumab-treated patients. This will need prospective validation.

**Timothy Eisen, MD, PhD, FRCP**
*Dr Eisen is Academic Clinical Lead; Professor of Medical Oncology; Honorary Consultant Medical Oncologist at Addenbrookes Hospital & Papworth Hospital and Director of the Cambridge Cancer Trials Centre, Cambridge, UK.*

The main buzz of ASCO renal data this year was again immunotherapy and others have commented extensively on this. There were also several useful additions to our knowledge of currently approved therapies, which should prompt further thoughts. The use of TKIs may seem so familiar that we have little more to learn. This is clearly incorrect as two papers involving the use of observation and TKI showed.

Rini and colleagues presented a prospective study of planned observation in a group of patients with relatively small volume asymptomatic metastatic renal cell carcinoma in systemic treatment-naïve patients and showed a median observation time of 14.1 months with 58% of patients still being observed after 1 year and 33% of patients still under observation after 2 years. For those patients this represents a massive saving of treatment toxicity. The only factor which appeared to predict the success of an observation strategy was a very low burden of disease (p=0.06). Patients with a total RECIST score ≤1.5cm had a median duration of observation of 31.6 months; patients with a total RECIST score > 1.5cm had a median duration of observation of 13.8 months. This suggests that asymptomatic patients with low volumes of disease should not be immediately treated with TKIs but should be observed. The one proviso I would add is that patients who are candidates for HD IL-2 should be considered separately from this group.

The second paper addressed the strategy of treatment breaks. This was a retrospective study which understandably largely involved patients who had done well on initial therapy. For some patients it is clearly a viable strategy to interrupt treatment for prolonged periods with the intention of restarting on significant progression. CR on prior therapy was associated with a prolonged period on observation in a treatment break. This strategy is being prospectively investigated in a UK study called STAR.

**Laura Wood, RN, MSN, OCN**
*Wood is the renal cancer research coordinator at Cleveland Clinic Taussig Cancer Institute in Cleveland, Ohio.*

ASCO 2014 was a very exciting meeting, as ongoing research efforts continue to identify potential new options for treating kidney cancer. Results from the ESPN Trial comparing everolimus and sunitinib in metastatic non-clear cell RCC were presented, with no clear winner between the two drugs. This was a small study (68 subjects) with very heterogeneous histological subtypes of non-clear cell. The ongoing ASPEN trial which compares everolimus and sunitinib in approximately 100 subjects and no cross-over has completed enrollment, and will provide additional information.

PD-1 and PDL-1 inhibition was a hot topic at ASCO with results on efficacy and safety of several agents being presented. nivolumab (BMS936558) and the combination of nivolumab with ipilimumab were presented, with very encouraging results. Pembrolizumab (MK-3475) results in other cancers were presented, supporting last year's presentation on MPDL3280A in renal cancer which support ongoing trials evaluating the potential benefits and safety of PD-1 and PDL-1 therapies in renal cancer.

As immunotherapy agents, PD-1 and PDL-1 inhibiting therapies have side effects that are very different from current therapies used to treat renal cancer. Adverse events may include fatigue, rash, diarrhea, neurologic, and changes in renal and liver function. Oncology professionals involved in the current clinical trials are gaining experience in the monitoring and management of these side effects.

It's very exciting to see additional progress being made, and the potential of new ways to treat advanced kidney cancer moving forward through the clinical trial process. As always, I encourage patients, family members, and health care professionals to refer patients with kidney cancer to sites participating in clinical trials. It is only through this process that we will improve the treatment options for patients fighting this disease. KCJ

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

# WHAT'S NEXT

**AFINITOR® (everolimus) Tablets is the first and only** oral mTOR inhibitor indicated for the treatment of adults with aRCC 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
- If symptoms are moderate, consider interrupting therapy until symptoms improve
- The use of corticosteroids may be indicated
- For grade 3 cases, interrupt AFINITOR until resolution to grade ≤1. AFINITOR may be reintroduced at a daily dose approximately 50% lower than the dose previously administered, depending on the individual clinical circumstances. If toxicity recurs at grade 3, consider discontinuation of AFINITOR
- For grade 4 cases, discontinue AFINITOR. Corticosteroids may be indicated until symptoms resolve
- 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 or candidiasis, 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

**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
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**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. 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. 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 or candidiasis, and viral infections including reactivation of hepatitis B virus have occurred in patients taking AFINITOR. Some of these infections have been severe (e.g., leading to 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.

### 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 RCC, 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]*.

### 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).

### 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.

## 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 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 RCC 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]*.

## 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.

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# Genetic Testing and Management in Early-Onset Kidney Cancer

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*Clinicians are often faced with young individuals with kidney cancer, some of whom may have a hereditary predisposition to this disease. Due to physician unfamiliarity with many of these syndromes and the lack of clear guidelines on genetic testing, most clinicians are not familiar with which patients should receive genetic counseling and how to initiate this process. Even when familiar with the conditions, there are multiple diagnostic challenges including an occult family history and subtle clinical features. However recent insights on the propensity for early-onset disease have changed the threshold when mutational testing should be considered because hereditary syndromes are suspected. For patients without an apparent cause for their kidney tumor, this does not exclude a complex inheritance pattern or genetic predisposition. Even for patients without any apparent cause of their kidney tumor, important principles of patient management should be considered prior to treatment.*

Underestimated and underrecognized are perhaps the two best terms to describe (1) the incidence of inherited renal tumors and (2) the need for genetic screening in renal cell carcinoma (RCC), particularly in patients with early-onset disease. Despite the possible benefit from germline or somatic mutation testing in many patients, there is a need for specific guidelines with simplified, hereditary RCC-specific referral criteria for genetic assessment. Within the last few years, new reports are offering a reassessment of current practices of germline genetic screening for hereditary RCC and are yielding important data with which to redefine referral characteristics of patients at risk, including their presentation, histology, prognosis, and likely outcomes.

It is unfortunate that this area has largely been overlooked by many clinicians because genetic testing is available for most of these syndromes, many of which have high RCC penetrance, other important disease manifestations, and established management strategies.[1] Identification of a single affected family member frequently leads to the diagnosis of a hereditary predisposition in other asymptomatic family members; surveillance can then be offered to these family members before any cancer develops.[2,3] The importance of understanding the genetic basis of an individual's predisposition has also been highlighted by other studies.[4,5] These reports have redefined management strategies in specific hereditary RCC syndromes. These strategies include specific recommendations on the role of nephron-sparing surgery, the method of partial nephrectomy (enucleation vs. margin), the timing of intervention, and renal mass surveillance.[6-8] There is still controversy, however, over which patients should be stratified into a high risk group for hereditary RCC and how to identify characteristics that would point the clinician toward a referral for genetic assessment and counseling. Recent reports are not only redefining these issues but suggesting a model that could be used to trigger consideration for germline and somatic mutation counseling, even in the absence of clinical manifestations and personal/family history.

RCC occurs in approximately 55,000 patients per year in the United States; hereditary RCC is estimated to account for 5% to 8% of kidney cancers.[9,4] This approximation may be grossly underestimated, based on a report in 2002 by Gudbjartsson et al who suggested that as much as 60% of patients with RCC may have some form of hereditary predisposition. The RCC syndromes include von Hippel-Lindau (VHL), hereditary papillary RCC (HPRC), Birt-Hogg Dubé (BHD), succinate dehydrogenase (SDH) kidney cancer, tuberous sclerosis complex, hereditary leiomyomatosis and RCC (HLRCC), Cowden syndrome, and microthalmia-associated transcription factor RCC. These syndromes may have similarities but differ in histology, aggressiveness and clinical manifestations.[10]

## Consideration for Germline Genetic Testing

When a known familial diagnosis of a hereditary syndrome is apparent, the need for mutational assessment is fairly straightforward. But patients may present with a previously unrecognized hereditary syndrome due to an occult or incomplete family history, subtle clinical features, incomplete penetrance, or a *de novo* germline mutation. In some patients, the absence of well recognized associated clinical manifestations may not suggest consideration of germline mutation testing. There are unique findings that should alert clinicians to a hereditary syndrome:

- Strong family history of RCC
- Bilateral/multifocal renal masses
- Associated clinical manifestations of known hereditary syndromes (eg, cerebellar hemangioblastoma in

VHL, cutaneous fibrofolliculomas in BHD)
- Specific renal tumor histologies (eg, hybrid/oncocytic RCC in patients with BHD)

Although there are many recent reviews of the clinical and genetic characteristics of hereditary RCC syndromes, recommendations for referral for genetic counseling and mutational testing are typically generic: they mention factors such as early age at presentation, bilateral tumors and family history.[11,12-16] Often lacking are specific details to the syndromes and this means the user needs to know or review each syndrome individually and their subtle associated manifestations.[1] Guidelines with simplified hereditary RCC-specific referral criteria for genetic assessment are needed. Similarly, a model that would encapsulate such criteria would be even more useful.

## Early-Onset RCC: the Importance of Age as a Risk Factor for Hereditary RCC

Kidney cancer has generally been considered a disease of old age with a median age of onset during the 7th decade of life. Analysis of standard incidence ratios (rate/100,000 individuals) demonstrates how unusual it is for kidney cancer to occur at a young age (**Figure 1**). As models defining early-onset kidney cancer have emerged, investigators have addressed concerns and questions in reviewing their own institutional experience and comparing that to data compiled by The Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute. Among the questions often framing the approach to genetic testing are the following:

- Is there an age threshold that can serve as a convenient guide to when germline and/or somatic mutation testing should be performed?
- To what extent do hereditary forms of RCC present at an earlier age than sporadic, nonhereditary forms of RCC?
- When the pathology report suggests translocation RCC or after negative genetic testing, what is the appropriate approach for further testing?

One of the recent reports to promote a reassessment of current practices of germline screening for hereditary RCC is the paper by Reaume et al[1] who proposed a guideline, the scope of which was to define the characteristics of patients in the general population (all ages) who are at risk for hereditary RCC and who should be referred. The recommendations from this Canadian group represent a broader guideline for the most common hereditary RCC syndromes and are based on a literature review and expert consensus. Early age at presentation, bilateral or multifocal tumors, and family history represent generic criteria that suggest a possible hereditary cancer syndrome irrespective of the organ involved.[14]

The age cutoff suggested by Reaume et al was derived from data presented by our group;[17] with data suggesting that 70% of hereditary RCC tumors would be found in the lowest decile (≤45 years old) of all RCC tumors.[17]

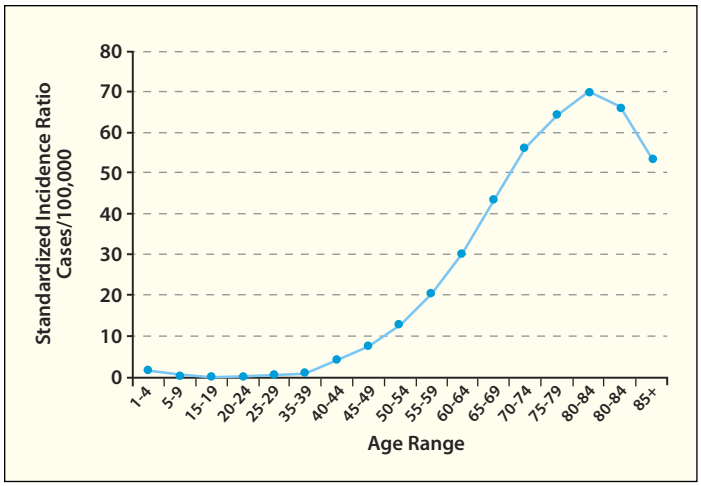


**Figure 1. Standardized Incidence Ratios of Kidney Cancer by age. Adapted from Howlader N, Noone AM, Krapcho M, Neyman N, Aminou R, Waldron W, Altekruse SF, Kosary CL, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Eisner MP, Lewis DR, Chen HS, Feuer EJ, Cronin KA, Edwards BK (eds). SEER Cancer Statistics Review, 1975-2008, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2008/, based on November 2010 SEER data submission, posted to the SEER web site, 2011.**

Reaume et al, however, do not make any recommendations regarding specific genetic testing methods or platforms. The group is seeking validation of its criteria and this will await additional information gathered by the new Canadian Kidney Cancer Information system collecting data on all RCC patients at 13 participating centers.

A more comprehensive analysis—utilizing both the SEER-17 program and our institutional analysis was published more recently and represents to our knowledge the first attempt to identify an evidence-based age threshold for RCC genetic testing as it provided a detailed delineation of the age distribution of kidney cancer in the United States.[10] Although studies of a number of RCC syndromes indicate a significant propensity for early onset,[18-19] no established RCC guidelines are available to aid in the selection of appropriate candidates for germline mutation testing.[10] The highlights of our report include the following:

- Hereditary forms of RCC present at a much earlier age than sporadic nonhereditary forms of RCC: median age of presentation for hereditary RCC was 27 years younger than that observed in the general kidney cancer population (as noted by SEER data) (**Figure 2**).
- Among individual syndromes, the median age of onset for kidney tumors in VHL, HLRCC, HPRC, and SDHB-RCC is lower than the 10th percentile of the general RCC population. BHD occurred at an older age than the other syndromes, but was still significantly lower than the general RCC population.
- Our model proposes that a useful threshold for genetic testing is around the 10th percentile (46 years of age or younger). This cutoff point maximizes sensitivity

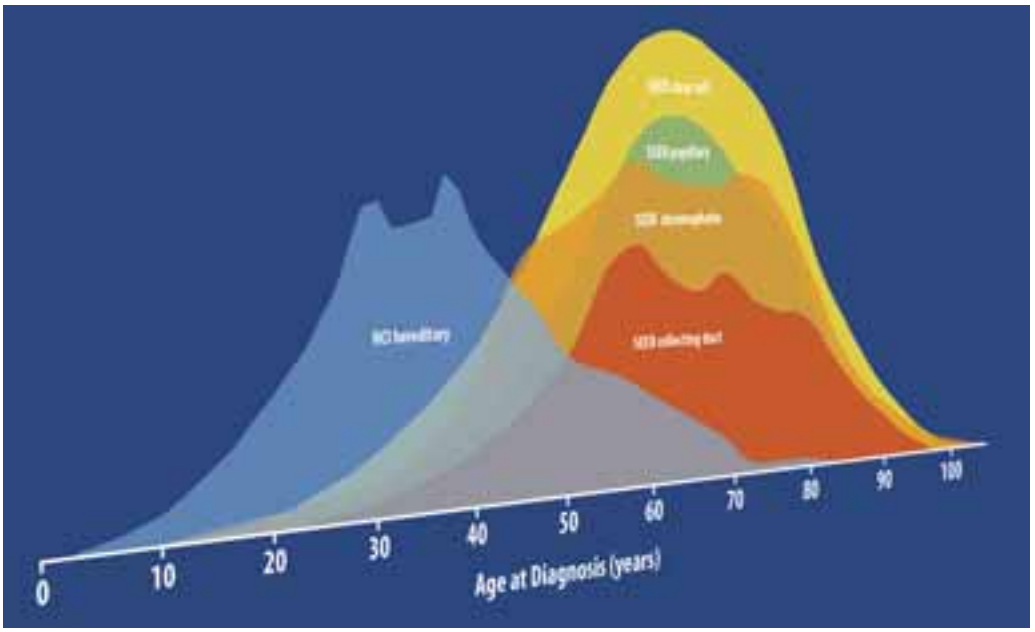


**Figure 2. Age distribution of hereditary kidney cancer cases compares the SEER registry by particular histologic subtypes. (Adapted from Shuch B, et al. *J Clin Oncol*. 2014; 32:431-437.)**

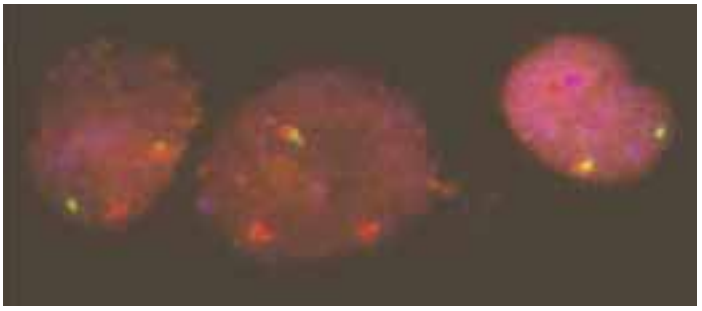

**Figure 3. FISH testing in a case of suspected translocation TFE3 Renal tumor. The break apart FISH probes (red and green) flank the Xp11.2 gene. With the translocation, one copy of the Xp11.2 gene locus translocates to various fusion partners leaving flanking probes no longer adjacent to each other.**

and specificity while limiting the number of patients needing to refer to genetic counseling and possibly test.

With these findings it is appropriate to further explore the implications for a wider application of genetic testing and suggest they have brought evaluation of younger patients closer to a new era for referral and assessment. One of the reasons for such optimism is the emergence of gene panel testing—an important breakthrough that could allow testing for all genes associated with hereditary RCC.[10] However, because the understanding of the difference between genetic variants and disease-causing mutations can be complicated, an experienced team versed in the intricacies of current clinical recommendations should take on this role.

An additional question addressed by our group concerns the role of somatic mutation testing in early-onset RCC. Distinctions need to be made from somatic and germline testing as it is important to differentiate between variants of RCC, since one entity, translocation RCC occurs in young individuals. Translocation RCC involves somatic fusion translocations and has no associated hereditary cause. It was first recognized in a fusion of the PRCC gene on chromosome 1 to the TFE3 gene on the X chromosome.[20] TFE3 is part of a family of transcription factors associated with RCC. Translocation RCC may affect 15% of patients with kidney cancer younger than age 45, and 20% to 45% of children and young adults who have kidney cancer. [21,22] Pathology can take various forms with papillary or nested architecture and the presence of granular and eosinophilic cells with voluminous, cytoplasm (Shuch, European Urology.[23] However cells can have classic clear cell pathology as demonstrated by The Cancer Genome Atlas finding of several cases with translocation despite conventional clear cell histology (TCGA).[24] When pathology suggests translocation RCC, fluorescent in situ hybridization (FISH) shouxld be considered as it has higher sensitivity than that of immunohistochemistry.[25] Our center at Yale now has a CLIA certificated molecular diagnostic test for testing of TFE3 translocations using break apart FISH probes (**Figure 3**).

At Yale, we have created a comprehensive program to evaluate those with suspicion for hereditary RCC including individuals with an early age of presentation (46 or less) (**Table 1**). However, if there was a concern for a translocation RCC, we evaluate with molecular diagnostics (FISH) prior to referral. If there is strong enough suspicion for testing for a specific genetic condition, we perform single gene testing, however if there is suspicion for various syndromes we perform in-house testing using an RCC gene panel which includes 14 genes associated with a hereditary predisposition to kidney cancer (**Table 2**). While panel testing isn't available at all centers, it may be the future of testing as this approach may limit cost and allow a quicker diagnosis compared to the traditional approach of sending testing separate genes in tandem.

### Bilateral/multifocal Kidney Cancer in Patients Without an Identifiable Predisposition

Even when a hereditary cancer syndrome cannot be identified, there still could be complex inheritance patterns contributing to an increased risk of bilateral or multifocal disease. An excess risk of cancer in a bilateral organ after unilateral disease has been well documented in various

**Table 1. Referral Criteria for Eligible Patients to Yale Genetic Counseling Program**

| |
|---|
| Kidney Cancer Age of Onset ≤46 years |
| Bilateral/Multifocal Kidney Tumors |
| Family History of Kidney Cancer<br>(≥1 first degree relative, ≥2 second degree relatives) |
| Kidney Cancer with Either<br>a) personal or family history of ≥1 tumor types*<br>b) lung cysts or pneumothorax |
| Unusual Skin Conditions<br>(such as Leiomyomas, Fibrofolliculomas, Angiofibromas) |
| Personal or Family history of a recognized kidney cancer syndrome |

*Pheochromocytoma, brain/spinal hemangioblastoma, pancreatic neuroendocrine tumors, retinal tumors, papillary cystadenoma, endolymphatic sac tumor, GI stromal tumors, uterine fibroids (≤30 years of age), uveal and cutaneous melanoma, and solid cancers occurring in childhood.

**Table 2. Yale Genetic Testing Kidney Cancer Panel**

| | | | |
|---|---|---|---|
| BAP1 | MET | SDHB | TSC2 |
| FH | MITF | SDHC | VHL |
| FLCN | PTEN | SDHD | |
| HNF1B | SDHA | TSC1 | |

cancer types, but it has taken longer for investigators to identify the extent of such risk in the kidney. The key is to identify patients early who are at greatest risk of developing bilateral RCC. In their review, Wiklund et al[26] based their findings on an average follow-up of 4.4 years in 28,642 patients obtained from Norwegian and Swedish cancer registry records. Compared with patients who were 60 years or older, those with a diagnosis ≤40 years of age had a 17-fold higher risk (RR=17.4) of bilateral RCC. The study adds to insights gained from other studies on the biology of RCC in other inherited cancer syndromes. In identifying this subset of early-onset patients with a possibly strong genetic predisposition, Wiklund et al suggest the findings could guide counseling and management of patients with unilateral RCC. The low excess and absolute risk of a contralateral cancer among older patients suggests little support for extensive monitoring of the unaffected kidney in this group after routine surveillance is completed. But in younger patients, histopathologic and genetic studies may identify those who need extensive monitoring because of their high risk for developing a *de novo* contralateral cancer or perhaps an ipsilateral lesion in those patients treated with partial nephrectomy.

The striking observations in the Wiklund report received additional focus in an editorial by Linehan[27] who suggests that the majority of patients with multiple/bilateral tumors have lesions that seem to arise independently. Linehan suggests that Wiklund et al[26] actually underestimate the true incidence of bilateral kidney cancer noting the relatively short duration of surveillance, only 4 years. A hereditary predisposition should lead to an expectation that additional kidney tumors may develop in these patients. Linehan also questions the estimates that 5% to 10% of renal cancers are hereditary, suggesting that this is a significant underestimate of the true hereditary predisposition to renal cancer. While the field currently recognizes over a dozen genes associated with hereditary kidney cancer, complex inheritance patterns likely contribute to cancer risk in this population but are unable to be ascertained with current genetic testing methods.

### Biologic Characteristics Associated With Early-onset RCC

The majority of patients with early-onset kidney cancer will not have a hereditary syndrome or a somatic translocation. However, these patients may also have unique biologic characteristics that should be recognized. There is still controversy in the literature, however, particularly in regard to differences in biologic characteristics in individuals with early-onset RCC, as noted by Thompson et al[28] in their report on RCC in young patients compared to their older counterparts. At the time their report was published in 2008, observations of younger patients with RCC (<40 years) was limited to approximately 700 patients in the literature. One important characteristic that has been demonstrated in multiple series is the increased frequency of non-clear cell tumors in individuals with early-onset kidney tumors.[29]

Thompson et al reported no significant differences in clinicopathologic characteristics for younger patients treated at Memorial Sloan-Kettering Cancer Center. Interestingly patients who were <40 years of age were more likely to present with symptomatic tumors. Conflicting data was presented by Sanchez-Otiz at M.D. Anderson and a multi-institutional cohort by Aziz, both demonstrating younger patients had either smaller tumors or lower T stage.[30,31] While this could be due to a less malignant potential, there is a possibility of lead-time bias since older patients may have tumors that are allowed additional time to grow prior to diagnosis. Sanchez-Ortiz also found that younger patients were more commonly found with lymph node involvement,[30] however other studies have been unable to confirm these findings.[28,29,31]

### Age of Presentation and RCC Prognosis

Several groups have addressed the issue of disease-specific survival in younger vs. older patients. While various authors suggest that younger patients (age ≤40) present with lower tumor stage than older patients,[29,31] there is still significant controversy over the influence of age on prognosis. Gillett et al compared younger patients with RCC to those with disease onset between 60 and 70 years old.

Although a trend was observed, the improvement in cancer-specific survival was not statistically significant.[29] Thompson similarly evaluated cancer-specific survival for patients treated with either partial or radical nephrectomy and found no significant differences between age groups.[28] Aziz used an international database of 2,572 patients with RCC to revisit the influence of age on prognosis. The multivariate analysis also showed that older patients had a higher disease-specific survival (hazard ratio: 2.21) and greater all-cause mortality (hazard ratio: 3.05). However, including age into a prognostic nomogram didn't appear to improve the ability to predict outcome.

One of the shortcomings of many of these studies examining the effect of age on prognosis is that the cut-offs used to assess this variable were not based on specific RCC biology and were adapted from the literature addressing other types of cancers with a different age distribution. Previous studies prior to 2008 were limited by sample size and methodology as most arbitrarily used a cut-point of age 40 to define early-onset. More recent data, however, have examined the issue through the prism of larger cohorts and applied more sophisticated analytic methodology. Karakiwicz et al,[32] included 3595 patients treated with surgery from 14 European centers. An analysis of prognosis by age of RCC diagnosis was performed using a cubic spline analysis instead of standard linear or stratified methods.

The key findings were:

- The risk of RCC-specific mortality was lowest among patients younger than 50 years, but RCC-specific mortality increased until the age of 50 years. At that point it reached a plateau.
- A second increase for the risk of RCC-specific mortality occurred in the group aged 75-89.

The unique feature of this study compared with earlier reports is its use of breakpoints in age as the analysis explored how these divisions influenced prognosis. The "take-home" message from this report is twofold: young patients can be reassured about their prognosis—stage for stage and grade for grade, they could have a better outcome after surgery.

## Specific Management Strategies in Young Patients With a Renal Mass

While most of the surgical principles and medical management of kidney cancer is similar regardless of age, there are several unique aspects of the care that a clinician should be familiar with. Though many in the urologic community do not embrace renal tumor biopsy, in a younger patient, this may be something that could perhaps affect management. Translocation tumors have a propensity for nodal involvement even for apparently localized tumors.[33] Suspicion of this entity on a biopsy would prompt many clinicians to consider a node dissection even in the setting of a localized tumor on imaging. A biopsy may be useful to guide genetic testing for those centers that have not embraced panel-based testing.[34] A diagnosis of a tumor with specific histology could assist in the decision of which gene to test for. Additionally if the tumor were small (< 3 cm) and localized, the results of genetic testing could guide patient management as well-established management strategies of active surveillance, which have been developed for syndromes such as VHL, BHD, and HPRC.

For tumor management, in older patients, small tumors could be treated with partial or radical nephrectomy in addition to ablative techniques. We recommend avoidance of ablation in young individuals with kidney tumors since long-term follow-up (>10 years) is not available. The success of ablation is also difficult to define, so patients may be subjected to many more years of surveillance imaging. With data on the potential harms of radiation exposure, this is something young patients must be weary of. Also the ability to salvage a patient must be considered since salvage partial nephrectomy after a failed ablation is a very morbid procedure with a much higher chance of radical nephrectomy.[35,36] Even if the ablation is successful, patients may have a *de novo*, ipsilateral renal lesion in another region of the kidney, similarly making surgery a challenging endeavor.

The decision to perform an elective radical or partial nephrectomy is also debated in the literature. There are several retrospective studies showing a survival advantage in patients treated with partial nephrectomy, however the only randomized control trial did not show superiority of a nephron-sparing.[37,38] There are limited series available to evaluate the outcomes of this question in younger patients, however one SEER analysis by Daugherty demonstrated improved overall survival at 10 years for patients age 20-44 with tumors ≤4 cm treated with partial nephrectomy[39] While this could also be due to non-measurable differences in patient groups, it does seem probable that the effects of chronic kidney disease are greater in individuals with a longer life expectancy. While living with one kidney has been considered safe and has set the precedent for living donor nephrectomy, recent data also suggests potential harms even in this patient population. Muzaale and colleagues demonstrated a small yet increased risk of developing end-stage renal disease in patients who underwent a donor nephrectomy when compared to participants in the Third National Health and Nutrition Examination Survey (NHANES III).[40] The median age of kidney donation in this population was 40.2, similar to the age of patients whom we consider to have early-onset RCC. While this represents a non-cancer population, it raises significant concerns that in young healthy patients with excellent life expectancy, every opportunity should be taken to preserve renal function with nephron-sparing surgery whenever technically feasible in order to maximize long-term renal function.

## Conclusion

The age of onset of kidney cancer is an important consideration in selecting patients for genetic counseling and

germline/somatic mutation testing. Although reports indicate approximately 5% to 8% of RCC is hereditary, this appears to be an underestimate in view of an increasing number of hereditary syndromes and recognition that many individuals may have a strong genetic predisposition that is not related to a single gene alteration. Even in the absence of clinical manifestations and personal or family history, an age of onset of 46 years or younger should signal consideration for genetic counseling and possible germline mutation testing. For other young individuals with kidney tumors, especially those with unusual histologic characteristics, a translocation RCC should be considered and confirmatory molecular testing performed. For those younger patients with no apparent cause of their kidney cancer, new reports are also redefining the clinicopathologic characteristics and outcomes When treating young patients with a renal mass, biopsy and genetic counseling may be considered if the results will change management. Localized tumors should be treated surgically with nephron-sparing surgery when feasible and ablation should be avoided due to concerns over difficulty with salvage/future renal surgery and lack of long-term outcome data.

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# Deconstructing the Sunitinib Treatment Paradigm: An Alternate Dosing Schedule Begins to Replace Standard Recommendations

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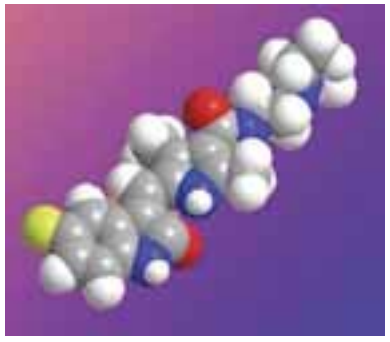
*Real-world clinical practice, particularly at academic centers and among many community oncologists, often moves at a faster pace than widely promulgated guidelines for using targeted therapies in advanced renal cell carcinoma. Emerging data from recent reports are revamping assumptions about the scheduling of sunitinib and raising some intriguing questions about the relationships between toxicity, response and how scheduling can prolong drug exposure while maintaining dose intensity. As these issues come under further study to validate the wisdom of an alternate schedule, it is time to reconsider how the algorithm is changing.*



**Artist's rendering of the sunitinib molecule.**

Dose interruptions. Intolerable adverse effects. Reduced exposure to drug and, ultimately, limited efficacy. These pitfalls are part of an ongoing treatment challenge in the era of vascular endothelial growth factor (VEGF)-targeted therapies. Such limitations to continued treatment are the result of a classic scenario—the adverse effects associated with first-line treatment with sunitinib, including hypertension, stomatitis, fatigue, hand-foot syndrome, and diarrhea as early as the first cycle of therapy in the traditional 4 weeks on 2 weeks off schedule. Although the era of VEGF-targeted therapies brought significant improvements in progression-free (PFS) survival, the tightly coordinated scheduling mandated for sunitinib offered a fairly limited number of choices of dose and scheduling that could be evaluated before FDA approval. Clinical trials leading to the approval of this agent did not provide for much flexibility in this regard. Hence, the traditional schedule became the standard approach for using this tyrosine kinase inhibitor (TKI).

But the paradigm of scheduling for sunitinib is evolving fairly rapidly. New results suggest an evolution in thinking with regard to the alternative schedules for sunitinib. And in that sense these new reports are deconstructing the paradigm for a drug that has long been a cornerstone of RCC management. The new line of thinking is based on a sound understanding of key predictors of pharmacokinetic and pharmacodynamic activity of this TKI,[1] as well as empirical observations on the breaches of normal tissue tolerance engendered by this agent that limit its use.

Sunitinib targets signaling by VEGF receptors, platelet derived growth factor receptors (PDGFRs), and KIT, among others; it is a current standard of care in the first-line treatment of untreated metastatic RCC.[2] The drug won its provisional FDA approval on the basis of hitherto unheard of response rates and PFS in phase II studies[3,4] and secured its approval following results from a phase 3 trial comparing sunitinib with interferon-alpha in patients with previously untreated mRCC. Sunitinib demonstrated significantly longer PFS than IFN-alpha (11 months vs 5 months).[5] The standard dosing schedule of sunitinib is 50 mg daily for 28 days, followed by 14 days

Keywords: Sunitinib, alternate dosing schedule, traditional schedule, adverse effects, drug exposure, duration of treatment.

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off drug (schedule 4/2).[2] This dose is based on preclinical data that the target plasma level of 50 ng/mL of sunitinib and its primary metabolite, SU12662, was maintained for at least half of the daily dosing interval at this dose and schedule.[3,5] Preclinical data indicate that target plasma concentrations of sunitinib and SU12662 in the range of 50-100 ng/mL were capable of inhibiting phosphorylation of PDGFR-beta and VEGFR-2; this suggests that this dose is the clinically significant range.

A report by Motzer *et al*[5] revealed the extent of toxicity associated with the maintenance dose of sunitinib. In this trial, 38% of patients required a dose interruption and 32% required a dose reduction secondary to adverse effects. The importance of maintaining an adequate dose of the drug was highlighted by Houk *et al*[1] in their retrospective analysis of 6 sunitinib trials: patients with the highest drug exposure (AUC) had longer overall survival, longer time to progression, and increased tumor burden reduction.[1] When viewed alongside the results by Motzer *et al*[5] showing the proportion of patients who need dose reduction/interruption, this inability to achieve adequate exposure to the drug may lead to lower plasma levels and reduced clinical benefit.

## Alternative Schedules: Continuous Daily Dosing Shows No Advantage

Efforts to identify the optimal algorithm for schedule and dose modifications to manage or prevent AEs has moved in several directions, beginning with two phase 2 clinical trials that demonstrated antitumor activity with sunitinib 37.5 mg continuous daily dosing.[6,7] Although initial results with this schedule tended to be encouraging, results by Motzer *et al* from the Renal EFFECT Trial[8] did not confirm the expected benefit. In this study, patients with mRCC were randomized to sunitinib 50 mg per day on the traditional schedule or to 37.5 mg continuous daily dosing for up to 2 years.[8] Median time to progression was 9.9 months for schedule 4/2 and 7.1 months for the continuous daily dosing schedule (*P*=0.90). No significant differences were observed in overall survival, commonly reported adverse events, or patient-reported kidney cancer symptoms. Schedule 4/2 was statistically superior to the continuous daily dosing schedule in time to deterioration, a composite end point of death, progression, and disease-related symptoms (*P*=0.34).

The data from Renal EFFECT suggest that continuous daily dosing was clearly not superior to the standard schedule of 4/2 of sunitinib for advanced RCC. Given the numerically longer time to progression with the approved 50 mg/day dose on schedule 4/2, the authors concluded that adherence to this dose and schedule should remain the treatment standard for patients with advanced RCC. Motzer *et al* provided a hint of future directions by recognizing the appearance of other alternative dosing schedules proposed for sunitinib. One of these is a pivotal trial conducted by Bjarnson et al.[9] Thus, after the findings by Motzer *et al* on continuous dosing, there was a need to assess new dosing strategies in randomized trials before implementing them over standard dosing programs in clinical practice.

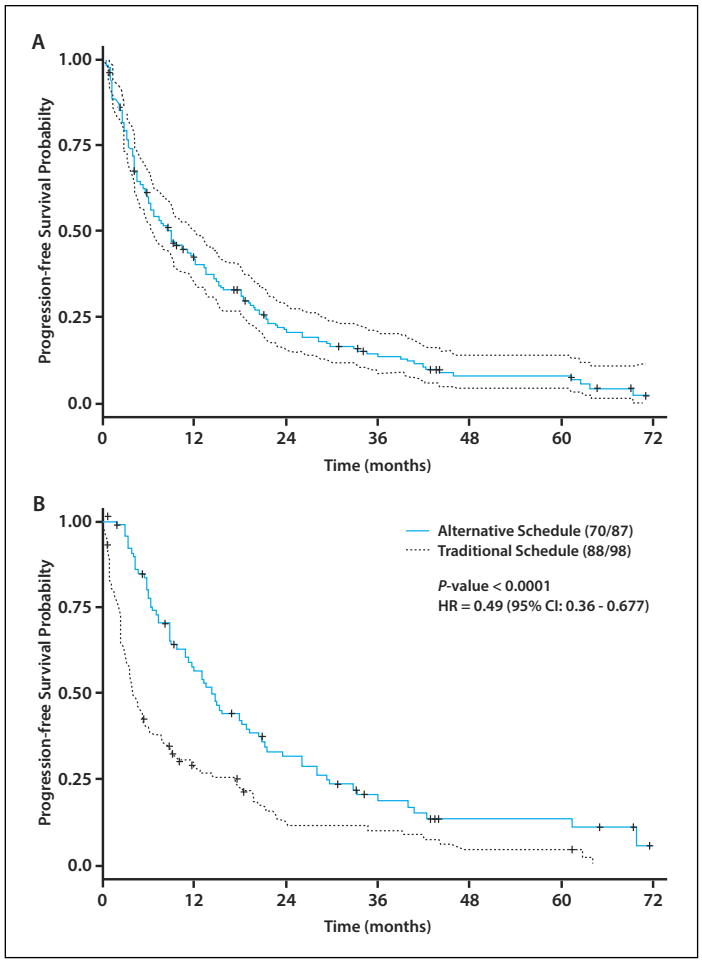


**Figure 1—Kaplan-Meier estimates in 185 patients from Atkinson et al.15 Of the 185 patients assessed, 158 (85%) had progressed or died by the last followup with a median PFS of 9 months, (A). Median PFS in patients on traditional schedule was 4.3 months and it was 14.5 months in those on the alternate schedule (B).**

Has this need been met? And, equally important, are we at a critical juncture in tailoring the use of sunitinib where many oncologists are already using alternate dosing schedules because this scheduling seems to be as active and perhaps more active as what can be achieved with rigid adherence to the standard 4/2 schedule? New results are suggesting that investigators are well on their way to deconstructing the algorithm of sunitinib scheduling. At many centers, including M .D. Anderson, a new paradigm is being followed. One of the questions surrounding the modification of the traditional schedule is whether an alternate schedule, which maintains dose intensity and the treatment to time off ratio, but shortens the treatment cycle, could translate into less time to develop the tissue-related toxicity that builds with longer exposure to the drug. The rationale is that with reduced duration of drug exposure, a patient would not need as much time to recover from the inherent toxicity associated with the traditional 4/2 schedule because the point where normal tissue tolerance is exceeded has not been


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**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)

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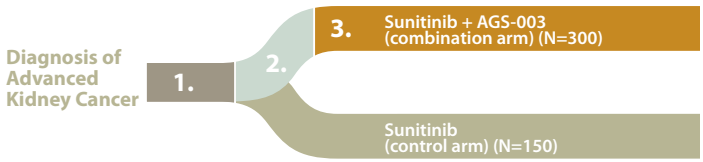
## **ADAPT** Study:




### 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)

Argos THERAPEUTICS

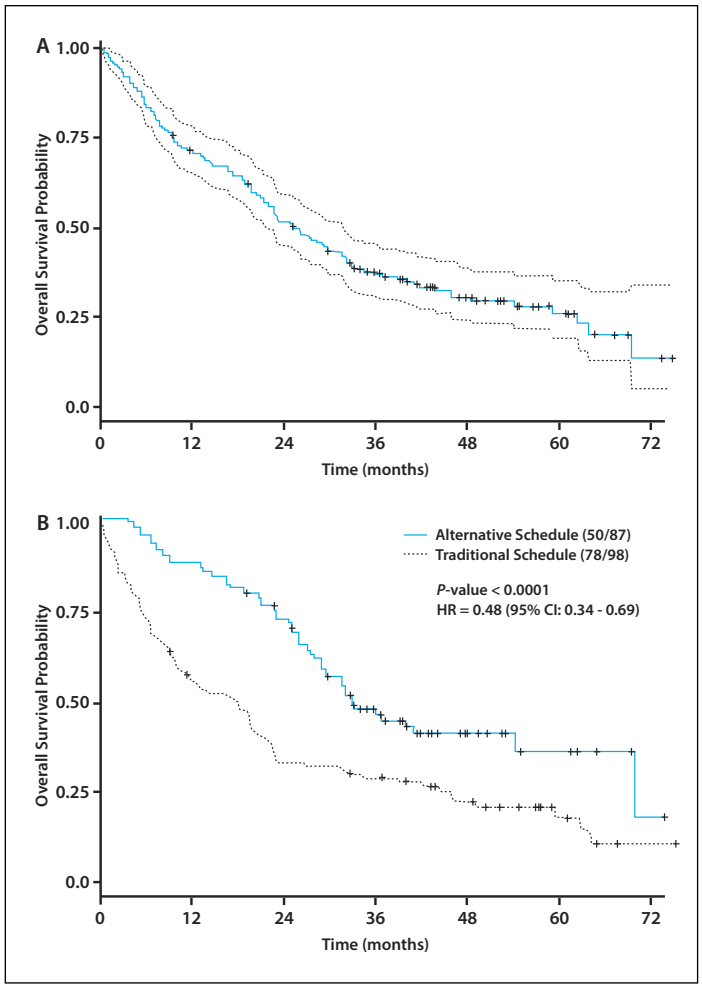



**Figure 2. By last followup, 128 patients (69%) had died with a median OS of 25.6 months (A). Median OS was 17.7 months for patients on the traditional schedule and 33 months for patients on the alternate schedule.**

reached. Thus, the time to treatment failure is prolonged because the side effect profile is improved while dose intensity is maintained.

## Alternate Dosing Schedules: 2 Weeks On and 1 Week Off

The gap between results generally achieved in registration trials and the real-world clinical experience tends to be underappreciated. As schedules with sunitinib come under closer scrutiny, there is a greater awareness of factors affecting the optimal use of various anticancer agents. Prasad et al, for example, point out how, in recent years, with the development of numerous oral anticancer agents, dosing options are arbitrarily and increasingly limited by the size of pills.[10] The authors note that an underappreciated consequence of pill size is unequal dosing in comparative clinical trials and that this can have an impact on outcomes. One of the issues investigators need to address is how comparative effectiveness trials can be unbalanced and how the use of doses that are not sustainable might affect outcomes, especially marginal ones. The matter is further complicated by poor tolerability and limited dosing options, according to Prasad *et al*. Since this often results in large dose adjustments in response to toxicity, the real-world clinical effectiveness of oral anticancer agents may be diminished and may not emulate results achieved in registration trials.

Although these issues are not at the core of new retrospective reports and are somewhat tangential to the discussion on the use of alternative dosing schedules, they suggest intriguing questions that arise within the context of various reviews and analyses as interindividual variability in sunitinib toxicity and activity are observed. To what extent, for example, are these differences between patients due to differences in sunitinib pharmacokinetics (PK), pharmacodynamics, and pharmacogenetics?[11,12] Motzer et al addressed this issue previously in 146 patients receiving the standard schedule of sunitinib.[8] There was no correlation between sunitinib PK values on day 29 (cycle 1) and the need for dose reduction based on toxicity; as a result, PK-guided dosing would not be helpful.[13] These issues led Bjarnason et al [9] to review outcomes for 172 patients with mRCC receiving sunitinib therapy using an individualized treatment strategy based on toxicity.

The single-center retrospective review used dose/schedule modifications (DSM) to keep toxicity (hematological, fatigue, skin, and gastrointestinal) at or less than grade 2. The schedules were: DSM-1, 50 mg, 14 days on/7 days off with individualized increases in days on treatment; DSM-2 was 50 mg, 7 days on /7 days off with individualized increase in days on treatment; DSM-3, 37.5 mg with individualized 7-day breaks; DSM-4, 25 mg with individualized 7-day breaks. The DSM-1 and 2 and DSM-3 and 4 groups had a PFS (10.9-11.9 months) and overall survival (23.4-24.5 months) that was significantly better than the PFS (5.3 months) and overall survival (14.4 months) for the standard schedule (50 mg, 28/14). Importantly, maximum antiangogenic activity was achieved after 14 days on therapy.

The finding that most of the benefit from sunitinib therapy is achievable after 7 to 14 days on therapy confirms pharmacokinetic data from several sunitinib trials in which blood levels for sunitinib reach a steady state at 10 to 14 days.[14] Bjarnason also found a rebound in vascular volume after a 2-week treatment break, supporting the use of a shorter 7-day treatment break. They also concluded that data on PK, reflecting the variability in PK slope and maximum value on day 14, further supports the concept of individualized dosing. One of the questions raised by Bjarnason *et al* is whether oncologists should begin to use the individualized scheduling before more prospective data are available. Yet this already appears to be the case.

Oncologists seeking additional validity for an alternative schedule to manage toxicity should consider the recent retrospective study by our group[15] as part of an initiative to maintain dose intensity while decreasing adverse events in patients with mRCC. An analysis based on data from 185 patients (mean age: 60 years) at the University of Texas M.D. Anderson Cancer Center com-

pared two groups: patients treated on the traditional 28 days on, 14 days off schedule, and a group of patients switched at the first intolerable adverse event from the traditional 28 days on and 14 days off schedule to a schedule of 14 days on and 7 days off or other alternative schedules. The key findings from this report:

- Median time on treatment in patients maintained on the 4/2 schedule was 4.1 months vs 13.6 months on the alternate schedule.
- Median PFS on the traditional schedule was 4.3 months vs 14.5 months on the alternate schedule (**Figure 1**).
- There was a median overall survival of 17.7 months on traditional scheduling and 33.0 months for patients on the alternate schedule (**Figure 2**).
- A decreased overall survival was more likely based on poor ECOG performance status, increased lactate dehydrogenase, decreased albumin, unfavorable Heng criteria and use of the traditional schedule.

Although by nature exploratory and hypothesis generating, this report by Atkinson et al[15] not only expands on observations from the earlier studies on alternate dosing, it offers additional insights on underlying factors that play a role in achieving the superior PFS and overall survival found in patients who switched from the traditional schedule. Despite maintaining essentially the same dose intensity as the traditional schedule, the incidence of adverse effects decreased as a function of schedule adjustment and this is an important consideration for any clinician opting for the alternate schedule. The role of adverse effects as a predictor of clinical efficacy and improved outcome has been addressed in previous reports. Rini et al[16] demonstrated that hypertension was linked to superior overall survival in 544 patients treated with sunitinib. There was also the observation by this group that antecedent hypertension was an independent predictor of improved outcome. Thus, perhaps an inherent dose independent, host specific characteristic predicts duration of response and overall survival in these patients. Additional evidence from Poprach et al[17] found a connection between skin toxicity and improved outcomes. In any case, the fact that adverse effects may be a sign of efficacy has contributed to speculation that a higher grade of toxicity is needed for increased efficacy.[17,18]

Atkinson et al, however, take a contrarian view to this supposition: as an alternate hypothesis they suggest that adverse effects may identify patients with inherent pharmacokinetic and pharmacodynamics characteristics that predispose to clinical benefit; the question then becomes whether toxicity may be managed by schedule changes without decreasing clinical benefit. This view makes sense in view of the finding by Atkinson et al that altering the dose with the alternate schedule may mitigate toxicity but does not appear to interfere with efficacy. If this can be validated, then a new insight is close at hand—perhaps toxicity is a marker of a response phenotype, but maintaining a higher level of toxicity is not necessary to achieve clinical benefit. As expected, there are limitations to the Atkinson report, notably the retrospective study design, including the inability to assess patient compliance with sunitinib and the possibility that adverse effects were not noted on electronic medical records. The authors also acknowledge that more patients with poor prognostic features were included in the traditional schedule cohort, a possibly limiting feature of the analysis. Nevertheless, the analysis provides additional evidence for a more dynamic approach toward toxicity management in patients receiving sunitinib.

Although the sample size was small, another retrospective review from the Cleveland Clinic[2] dovetails with the findings from M.D. Anderson with regard to the benefits of the 2 weeks on and 1 week off schedule. The review of 30 mRCC patients revealed that 97% of patients on schedule 4/2 had grade 3 or 4 toxicity that led to changing to schedule 2/1. Following the switch, the prevalence of adverse effects diminished significantly:

- There were no grade 4 toxicities on schedule 2/1, and 27% of patients experienced grade 3 toxicity.
- Two of the most common toxicities, fatigue and hand-foot syndrome were significantly less frequent on schedule 2/1 than on the traditional schedule.

## Conclusion

The paradigm with targeted therapies that has grown out of a decade worth of experience is to maintain dose intensity whenever possible. The adverse effects associated with the traditional dosing schedule of 4 weeks on and 2 weeks off for sunitinib has been reexamined in the light of new data suggesting that an alternate dosing schedule of 2 weeks on and 1 week off maintains efficacy while reducing the severity of adverse effects. This schedule is now being followed at leading academic centers and by many oncologists to maximize dose and minimize time without therapy for patients who cannot tolerate the standard sunitinib schedule. An ongoing trial at 5 centers In the U.S. (NCT02060370) and another in Canada (NCT01499121) have been launched to further study the benefit of alternate schedules. As the results of these studies are awaited, the expanding use of alternate sunitinib schedules raises questions about the use of other oral agents and whether an opportunity is being missed to improve quality of life in mRCC by evaluating other alternate dosing schedules in these therapies to maintain drug exposure while minimizing adverse effects.

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# Let's Reappraise Small Renal Cortical Neoplasm Biopsy, Debunk the Myths Surrounding It, and Optimize Its Potential

*The role of renal mass biopsy has been expanding, driven by the knowledge that at least 20% of the tumors have benign or relatively indolent pathology. The discovery and characterization of new molecular markers suggest the technique should be more widely used. But misconceptions about renal biopsy still persist and we need to reconsider its benefits in the light of fresh data. In this interview, Jaime Landman, MD, Professor of Urology and Radiology, and Chairman, Department of Urology, University of California Irvine, addresses the salient issues on how renal biopsy can be used to make more informed decisions about definitive management.*

**Q:** Why is a biopsy still not considered a standard modality for the small renal mass?

**Dr Landman:** The reason for this is fourfold. The first reason is historical: in the past clinicians diagnosed small renal cortical neoplasms differently than is the case today. Today, approximately two-thirds of these small tumors are found incidentally and the patient tends not to have symptoms at all. Often, patients diagnosed with these small tumors have an ultrasound, an MRI or a CT scan for a reason completely unrelated to the kidney lesion, and a small tumor is identified. There is good evidence that these tumors are a different "species" than what was found in the past. Many of these tumors are never destined to be clinically manifesting themselves. Currently, the lion's share of renal tumors that are identified are less than 4 cm (cT1a). In the past, urologists would generally only identify larger, more significant tumors that needed to be treated with an appropriately aggressive approach — radical nephrectomy. Today many of these small renal masses (which via biopsy are demonstrated to be less aggressive cancers) are better treated with observation or with significantly less invasive treatment options, perhaps with an outpatient procedure such as percutaneous ablation. Biopsy also allows for increased application of nephron sparing approaches which are critical for preserving patient's long-term cardiovascular health.

**Q:** What about the technological advances? Are they a factor?

**Dr Landman:** Historically biopsy techniques were not what they are today and did not yield as high sensitivity and specificity. Today biopsy yields much better results and can better differentiate benign from malignant tumors. The new biopsy techniques are more reliable and the information can be used to manage patients whereas in the past this was not the case.

**Q:** Are complications a significant issue with renal biopsy? Is tumor seeding an issue?

**Dr Landman:** Previously the biggest concern was seeding or spreading of the tumor; there have been 11 cases of seeding in the world's body of literature. Of those 11, only 2 have occurred since 1991. The idea of tumor seeding (one in 10,000 would be an exaggeration of the extent of risk) should not preclude the decision to perform biopsy. In every other solid tumor except that within the kidney, biopsy is the standard. It is most unfortunate and disappointing that we have strayed away from renal tumor biopsy based on what is largely a theoretical concern.

**Q:** What about the influence of surgery? Does the rationale for various interventions affect the decision to perform a biopsy?

**Dr Landman:** Yes, there is tremendous enthusiasm for intervention in the form of different surgical procedures, including laparoscopy, robotic surgery and ablation. Really, we have never before had such a protean variety of treatment options available in our armamentarium. We now know that contemporary biopsy technique is good and will provide reliable results without complications. Biopsy not only helps with the binary decision of surgery versus observation for cancer versus benign disease but should help guide the urologist and patient toward which treatment option is best suited to the patient's particular biology.

**Q:** Has there been a change in perception regarding the biology of renal masses?

**Dr Landman:** Absolutely. We know more about the biology of the disease: not only do we not have to treat benign tumors most of the time, in a certain percentage of renal cell carcinomas (RCCs) treatment is also not required because they are very indolent malignancies that are slow growing tumors like papillary type 1 or chromophobe tumors. In the older patients with significant comorbidities, there may be no need for treatment for the indolent malignancy. In these tumors, active surveillance is appropriate.

**Q:** To what extent is a repeat biopsy required, and what are the advantages of doing so?

**Dr Landman:** In the past repeat biopsies were rarely done because we had a poor conviction of the concept of biopsy to begin with. However, if a biopsy fails—which can happen—and let's say, 20% of the time we do not get adequate tissue or there is an indeterminate result, then patients do need a repeat biopsy. Very few patients do not have a meaningful result from their biopsy after two attempts.

**Q:** Are you saying that a biopsy should be done on any suspicious mass?

**Dr Landman:** In the majority of patients, biopsy should be the default setting. However, there are exceptions. For example, if you identify a tumor in a very sick patient, no matter what the biopsy shows, you are not considering surgery in that patient. There is very little need to do a biopsy in this context. But the default setting in most other cases in the US and in the world has been no biopsy. Only 6% of patients in the US are getting biopsies in contemporary practice. The converse numbers should be true—94% of patients probably do need a biopsy and it would be extremely helpful in the proper management of their renal cortical neoplasm. There is a small percentage where it will not make a difference if they do not have a biopsy.

**Q:** There still seems to be resistance, then, on the part of the community oncologist? What's actually happening out there in the real world?

**Dr Landman:** In many cases in my practice, which are largely second opinion cases, I always need to backtrack with the patient because the referring urologist or oncologist has often shared with the patient the historical dogma—that you do not biopsy renal tumors. With the minimal risk of seeding and complications, the increased accuracy of biopsy in predicting the patient's disease, and the numerous treatment options that are currently available, renal cortical neoplasm biopsy is increasingly important.

**Q:** Would you say there is a relatively high rate of technical biopsy failures? An article in the *Journal of Urology* seems to indicate that this may be the case.

**Dr Landman:** Realistically, a certain percentage of patients will need repeat biopsy only because they do not get a diagnostic biopsy. If you look at the literature, it shows that a second biopsy will be necessary in up to 20% of patients. However, very few patients remain without a clear diagnosis after two biopsies.

**Q:** How will some of the advances in biopsy techniques such as fluorescent in situ hybridization enhance the use of biopsies?

**Dr Landman:** As strongly as I feel that biopsy is important today, I am utterly convinced that with these novel technologies, the use of biopsy will be even more of a no-brainer tomorrow and we will obtain less equivocal results. Molecular biology is increasingly being incorporated into routine clinical practice with wonderful results. RNA-based biopsy techniques will be more accurate. For example, one of the criticisms of biopsy is that it cannot separate an oncocytoma, from a chromophobe renal cell carcinoma. It's interesting because I do not think that in a majority of cases, that makes a difference. A very small chromophobe is a very indolent malignancy that does not have a terribly different biological behavior in most cases than a completely benign oncocytoma. In the near future we should be able to easily distinguish these two on molecularly enhanced biopsies.

"There is a renaissance in molecular biology and its clinical application that is vastly going to be incorporated into the standard biopsy technique. So our ability to distinguish among different types of tumor and our ability to detect tumors should improve rapidly in the future."

**Q:** Then fluorescent in situ hybridization could have a significant impact?

**Dr Landman:** In the end, that will wind up vastly improving our ability to diagnose different renal lesions, and yes, all the subtle differences between tumors. A lot of the tissue today is considered nondiagnostic. I believe our ability will improve vastly as we start looking at the biopsy tissue that we are taking with molecular techniques.

**Q:** Overall, you sound optimistic and suggest that there is a renaissance in the use of renal mass biopsies?

**Dr Landman:** Absolutely. There is a renaissance in molecular biology and its clinical application that is vastly going to be incorporated into the standard biopsy technique. So our ability to distinguish among different types of tumor and our ability to detect tumors should improve rapidly in the future.

**Q:** Can you identify which patients should not undergo biopsy?

**Dr Landman:** A patient should not undergo renal cortical neoplasm biopsy when the procedure does not impact the decision-making process. If we objectively think about the information typically provided by biopsy, in the vast majority of cases renal cortical neoplasm biopsy is indeed indicated.

**Q:** So would you say no patient should be deprived of biopsy?

**Dr Landman:** I would not say that. I would say only a small number of small renal cortical neoplasms do not need biopsy. Sadly, I do think that we need the converse of contemporary biopsy. Currently, about 6% of small renal cortical neoplasms are being biopsied. In the course of thoughtful treatment strategies, I would estimate that 94% of these tumors should be biopsied and only 6% of cases should be managed "blindly."

**Q:** One last question: is the use of targeted therapy in any way a factor in why biopsies are not generally done?

**Dr Landman:** I do not think that is involved in the decision-making process. Targeted therapy is used in the setting where we are not talking about these small renal tumors. KCJ

# A Data-Driven Look at Renal Mass Biopsy: Informed Treatment Decisions With Its Routine Use

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If there is one practice pattern that seems to defy logic—or at least flies in the face of the overwhelming evidence in the literature—it is the failure to perform renal mass biopsy (RMB) routinely or at least in more cases, and then using this information to implement definitive treatment strategies. Concerns about high false-negative rates, complications, and the risk of seeding have largely stood in the way of clinical practice catching up with the contemporary results in the literature which strongly support the practice of renal mass biopsy.

The expanded use of imaging including computerized tomography (CT) and ultrasound for a variety of abdominal complaints has led to the incidental detection of more renal masses, many of them smaller than was the case before the less prevalent use of these imaging modalities. Up to 66% of RCC is now detected incidentally;[1] approximately 20% of the small, solid, enhancing renal masses detected on CT are benign tumors.[2] In view of the clinical and histological heterogeneity of renal cortical neoplasms, there is a need for more information on the potential aggressiveness of these neoplasms, thereby facilitating important findings with which to risk stratify patients and enhance clinical decision making. Yet, until recently, the role of renal mass biopsy and fine needle aspiration has been limited. Primarily it has been used to rule out nonrenal cell primary tumors (metastasis and lymphoma) or benign conditions that may not require surgery.

A dramatic change continues to occur in our view of renal mass biopsy. One study refers to a "renaissance" in the use of the technique and, finally, at least in the literature, a growing recognition of its routine value. The evolution in thinking is reflected in many reports. For example, those concerns about false-positive rates of up to 25% have faded because it is now clear that many false-negatives in these earlier reports were in fact instances in which the mass could not be adequately targeted or the material obtained was insufficient for the pathologist to make a definitive determination.[3] As Lane et al report: serious complications of percutaneous biopsy are rare and the minor complication rate in recent series has been less than 5%. The reported rate of technical failure of renal mass biopsy due to insufficient material was about 9% before 2001 and 5% in more recent studies. The likelihood of indeterminate or inaccurate pathological findings has decreased from 10% to 4% when comparing clinical studies before and since 2001. A total success rate of 90% is attainable using renal mass biopsy with standard histopathological analysis and the false-negative rate is less than 1%.

Lane et al offered recommendations:

- Young and healthy patients who are unwilling to accept any uncertainty with conventional RMB are still best treated with surgical excision.

Keywords: renal mass biopsy, false-negative, percutaneous needle core biopsy, fluorescence in situ hybridization.

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- RMB should not be used to justify nonoperative management in anatomically challenging cases, solitary kidneys or patients with impaired renal function.

The accuracy of RMB for distinguishing benign from malignant tumors has improved and shown to be 94% overall with reported sensitivities ranging from 80% to 92% and specificities from 83% to 100%.[4,5]

One of the other major concerns—tumor seeding—has also not turned out to be a significant consideration as a complication of RMB. It has a reported incidence of less than 0.01% with only a single case reported since the early 1990s.[6] Thus, the propensity of RCC to metastasize via tumor seeding is no greater than that of other malignancies where pre-treatment biopsy is standard of care. However, one cautionary note is advised in this regard: the potentially higher risk of spread with transitional cell carcinoma means that biopsy should not be performed for infiltrative central renal masses when transitional cell carcinoma is suspected.[7]

### Small Renal Mass: How Aggressive?

More information is now available on the natural history of small renal masses, although partial or radical nephrectomy is often performed soon after detection. Abundant evidence suggests that tumors measuring 3 cm or less rarely metastasize and have a slow growth rate.[8-10] An early study by Rendon et al who followed 13 patients with small renal masses unsuited for or refusing surgery reported that the tumors that were destined to grow fast and possibly metastasize did so early, whereas most small tumors grew at a low rate or not at all.[11] Expanding on these observations, Volpe et al[12] followed 29 patients for a median of 27.9 months. The implication from this study was that approximately one third of small renal masses presumed RCCs grow if they are managed conservatively and are followed with serial imaging. The growth rate is slow or unde- tectable in most patients, thus supporting a period of initial observation in selected patients, especially the elderly or those with co-morbid conditions. Surgical treatment is advised for patients who have tumors with rapid doubling times or tumors with volumes or bidimensional measurements that reach a threshold demonstrated as unsafe. In their review, Volpe reported that an upper limit of 3-5 cm in greatest dimension is used commonly to identify renal masses at very low risk of developing metastases. Survival rates tend to be better in this subset.

Volpe et al also allude to the limitations of imaging and the pitfalls in relying too heavily on such modalities to follow patients with small renal masses. They report that tumor growth rate determination alone probably will not give clinicians enough information to predict accurately the behavior of these masses. Cytogenic, immunohistochemical or other investigations done on needle biopsies could play a larger role. Nevertheless, imaging is still one of the cornerstones since they suggest that new radiologic parameters using CT scanning and MRI may be helpful in identifying patients who have renal tumors with good prognostic factors and who therefore could be followed conservatively.

One of the key advantages of preoperative needle core biopsy is its accuracy to diagnose benign specimens among small incidental asymptomatic renal masses. A report by Shannon et al[5] analyzed results from 235 preoperative core biopsies from 222 less than 5 cm; biopsy results were correlated with surgical specimen final pathology findings or with patient followup if surgery was avoided. This study, purportedly the largest study of core biopsy for small renal masses, revealed:

- Of 194 tumors identified biologically by biopsy and/or renal surgery, 48 (25%) were diagnosed as benign despite being considered likely malignant by radiological analysis.
- This high proportion of benign lesions justifies preoperative histological diagnosis to decrease the rate of unnecessary renal surgery.

A key question addressed by Shannon et al concerns the failure rate for biopsy observed in a previous report,[4] partly due to more difficult visualization and targeting and the biopsy needle displacing small masses rather than penetrating them.[13] This study mitigates the problem significantly by taking multiple needle cores per tumor rather than a single core. It is possible to further improve the failure rate, according to other reports, by assessing core quality and performing immediate rebiopsy when the specimen was torn or less than 10 mm long and by obtaining at least 2 whole needle cores per tumor.[14,13]

The issue of repeat biopsy in patients with a prior nondiagnostic biopsy of the same mass is also an important issue, particularly because some clinicians may erroneously feel reassured that a nondiagnostic biopsy of a suspicious mass is a surrogate for the absence of malignancy. This is not necessarily true, according to Leveridge et al[15] whose retrospective study that confirmed the efficacy and outcomes of renal mass biopsy (RMB) in a large series of small renal masses, sought to better define the outcomes with nondiagnostic biopsy and explored outcomes of repeat biopsy. This Canadian analysis based its findings on a database of 345 biopsies, 80.6% of which were diagnostic and nondiagnostic in 19.4%. Repeat biopsy was performed in 12 of the 67 nondiagnostic cases and a diagnosis was possible in 83.3% of these cases. Pathology was available for 15 masses after initial nondiagnostic biopsy; 11 or 73% were malignant.

The "take-home" message from the study by Leveridge et al was that the diagnostic rate on rebiopsy was similar to the initial biopsy rate, and 80% were cancers. According to their report, there is nothing intrinsic to these tumors themselves that results in a nondiagnostic biopsy and that repeat biopsy is both feasible and can be expected to identify tumors and cancers. The feasibility and accuracy of repeat biopsy needs to be further studied, but related data from Laguna et al[16] add further support for the diagnostic accuracy of repeat biopsy. A nondiagnostic

biopsy should not be considered evidence of a benign lesion because in many of these cases, when tissue becomes available, cancer is detected on repeat biopsy at a rate similar to those with an initial biopsy.

### Future Directions: FISH Can Enhance Accuracy

As molecular technology enhances the diagnostic accuracy of biopsy, the use of fluorescence in situ hybridization (FISH) can be expected to play a greater role in determining the subtype of RCC on needle core biopsies. FISH analysis is a useful tool that facilitates differentiation between tumor types. This remains particularly important in cases of renal tumor biopsies when limited tissue is available for analysis and the results are required to inform a conservative nephron-sparing surgical approach.[17] As histological subtypes of RCC have distinct cytogenetic abnormalities (loss of 3p in clear cell, trisomy 7 or 17 in papillary and widespread chromosomal losses in chromophobe), Barocas et al hypothesized that FISH could improve the accuracy of biopsies.

The results tend to validate the utility of FISH in improving the accuracy of needle-core biopsies:

- 40 patients underwent nephrectomy, yielding 42 tumors, and needle-core biopsies taken of the mass immediately after surgery.
- FISH was performed on one core for chromosomes 3, 7,10, 13, 17, and 21 and the locus 3p25-26. Histopathology was performed on a second core and results compared.
- 36 of 42 masses were RCC or oncocytoma; histopathology of the biopsy correctly identified tumor subtype in 75% while 11% were incorrectly classified and 14% were inadequate for diagnosis.
- With the addition of FISH, 86% were correctly subtyped while 6% were incorrect and 8% were inadequate. When tissue was adequate histology alone was 87% accurate while the combined methods were 94% accurate.

### Conclusion

Indications for renal mass biopsy have been expanding as treatment options for renal cortical neoplasms have grown and as the safety and efficacy of RMB have been demonstrated. The limitations of imaging alone to conclusively determine malignancy suggests that RMB can provide additional helpful information in risk stratification and clinical decision making. Its routine use in the management of small renal cortical neoplasms should be incorporated as part of the clinical algorithm,

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GUEST EDITOR'S MEMO *(continued from page 38)*

effectively tailored to minimize the drug's adverse effects while maintaining optimal outcomes, thereby prolonging duration of therapy.

- A reappraisal of the role of renal mass biopsy by Jaime Landman, MD, whose report demythologizes the traditional thinking about biopsies and suggests how molecular advances have ushered in a new era for this procedure.

I wish to gratefully acknowledge the work of my colleagues in providing content that meets the educational needs of our audience of medical oncologists and urologists.

**Jose A. Karam, MD**
Guest Editor

GlaxoSmithKline

**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.**

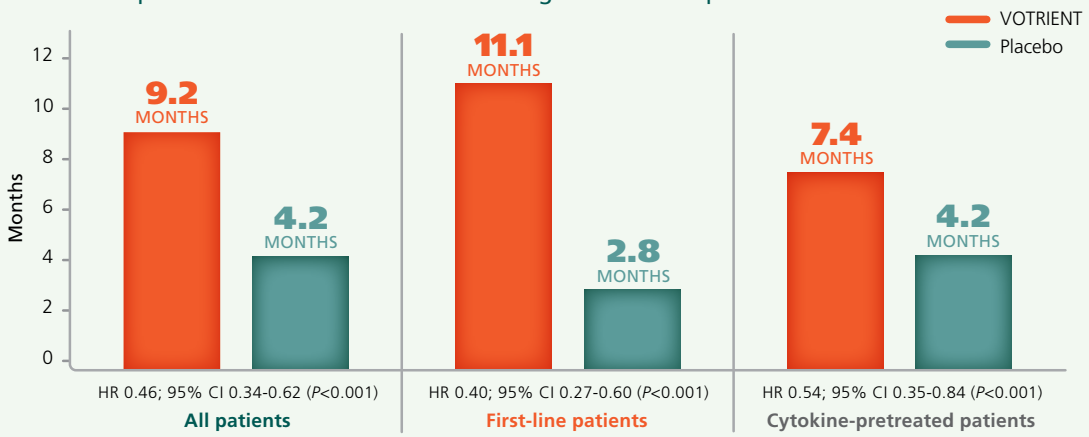
Votrient®
pazopanib tablets (200 mg)

**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]

Median PFS in patients with advanced RCC receiving VOTRIENT vs placebo[1,2]




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.

## 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.**

**VOTRIENT (pazopanib) 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 VOTRIENT (pazopanib) as first-line treatment options.

- **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 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.
- **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; 2013. **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 V.2.2014. ©National Comprehensive Cancer Network, Inc. 2013. All rights reserved. Accessed December 9, 2013. 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.**

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

**www.GSKSource.com** **VOTRIENT.com/HCP/aRCC**

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

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

Other adverse reactions observed more commonly in patients treated with VOTRIENT than placebo and that occurred in <10% (any grade) were alopecia (8% versus <1%), chest pain (5% versus 1%), dysgeusia (altered taste) (8% versus <1%), dyspepsia (5% versus <1%), 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) | | |
|---|---|---|---|---|---|---|
| **Parameters** | **All Grades[a] %** | **Grade 3 %** | **Grade 4 %** | **All Grades[a] %** | **Grade 3 %** | **Grade 4 %** |
| **Hematologic** | | | | | | |
| Leukopenia | 37 | 0 | 0 | 6 | 0 | 0 |
| Neutropenia | 34 | 1 | <1 | 6 | 0 | 0 |
| Thrombocytopenia | 32 | <1 | <1 | 5 | 0 | <1 |
| Lymphocytopenia | 31 | 4 | <1 | 24 | 1 | 0 |
| **Chemistry** | | | | | | |
| ALT increased | 53 | 10 | 2 | 22 | 1 | 0 |
| AST increased | 53 | 7 | <1 | 19 | <1 | 0 |
| Glucose increased | 41 | <1 | 0 | 33 | 1 | 0 |
| Total bilirubin increased | 36 | 3 | <1 | 10 | 1 | <1 |
| Phosphorus decreased | 34 | 4 | 0 | 11 | 0 | 0 |
| Sodium decreased | 31 | 4 | 1 | 24 | 4 | 0 |
| Magnesium decreased | 26 | <1 | 1 | 14 | 0 | 0 |
| Glucose decreased | 17 | 0 | <1 | 3 | 0 | 0 |

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

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.

**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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*(continued from page 59)*

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