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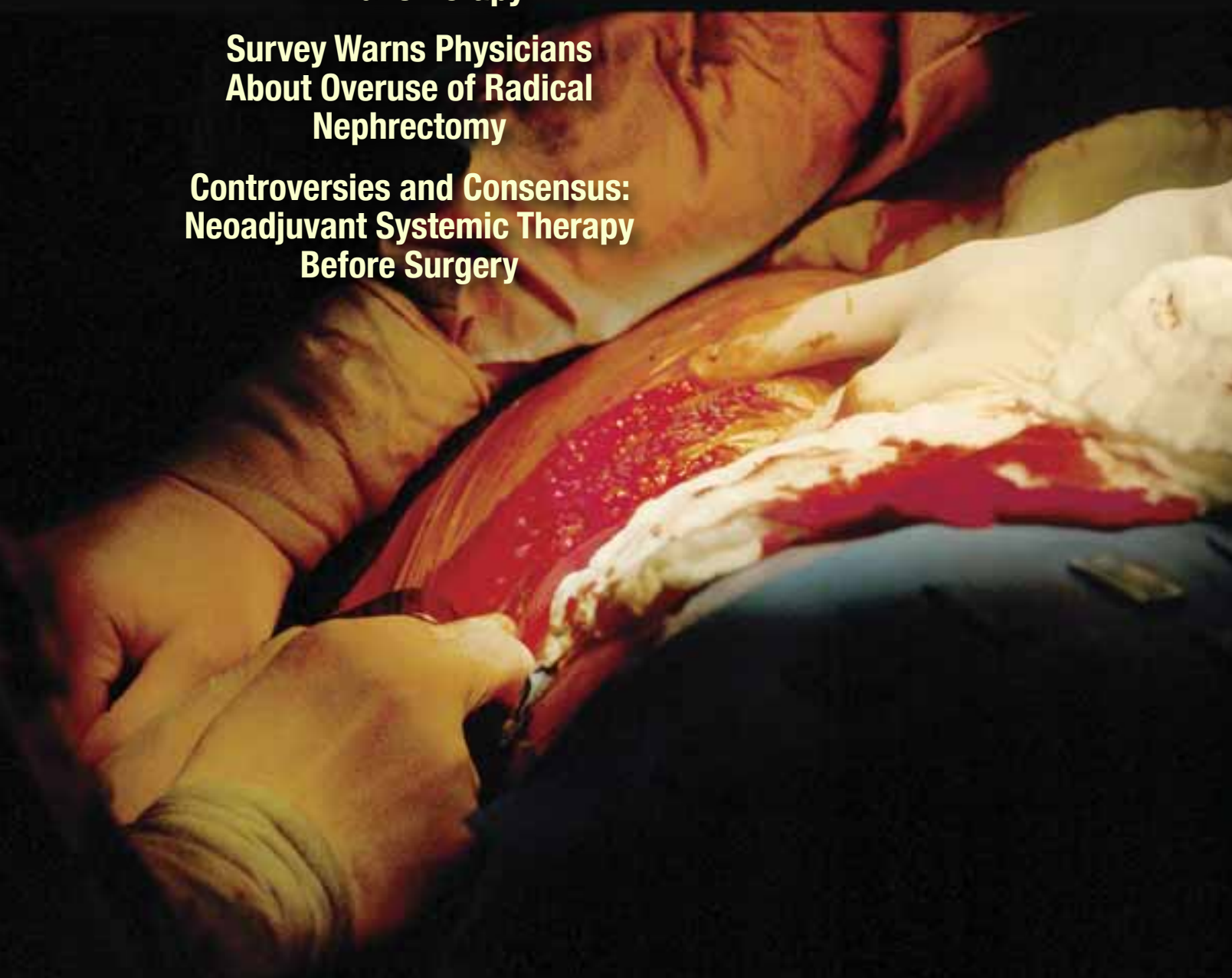
Future Directions: Inhibiting Autophagy to Enhance Effectiveness of Immunotherapy

Survey Warns Physicians About Overuse of Radical Nephrectomy

Controversies and Consensus: Neoadjuvant Systemic Therapy Before Surgery



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.

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.

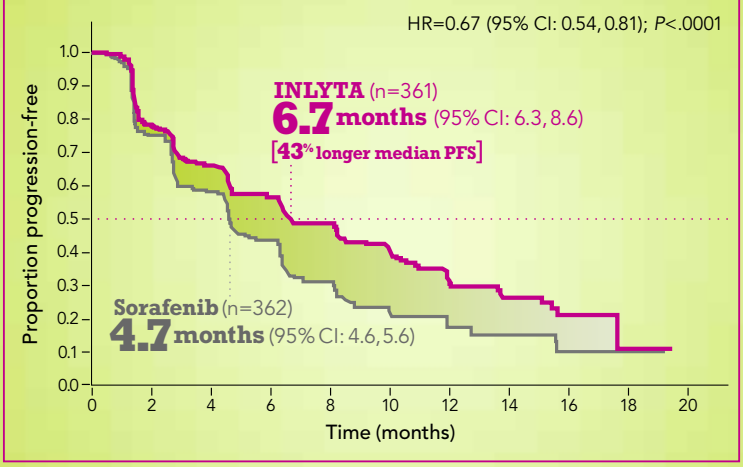
INLYTA®

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

PROOF OF SUPERIOR EFFICACY VERSUS SORAFENIB IN 2nd-LINE mRCC

IT MATTERS.

Superior progression-free survival (PFS) vs sorafenib



Data are from a multicenter, open-label phase 3 trial of 723 patients with metastatic renal cell carcinoma (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 twice daily) with dose adjustments allowed in both groups.[1]

More than doubled objective response rate[1]

- 19.4% vs 9.4% with sorafenib
  - –95% CI: 15.4, 23.9 and 6.6, 12.9, respectively
  - –Risk ratio: 2.06 (95% CI: 1.41, 3.00)
- All responses were partial responses per RECIST criteria

INLYTA has been shown to inhibit receptor tyrosine kinases, including VEGFR-1, -2, and -3 in vitro and in preclinical models

- Preclinical activity does not necessarily correlate with clinical outcomes

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 page.

Inlyta™
axitinib 1mg and 5mg tablets

Data are from a multicenter, open-label phase 3 trial of 723 patients with metastatic renal cell carcinoma (mRCC) after failure of 1st-line therapy (sunitinib-, temsirolimus-, bevacizumab-, or cytokine-containing regimens). Patients were randomized to either INLYTA (5 mg twice daily) or sorafenib (400 mg twice daily) with dose adjustments allowed in both groups.

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.

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 *[see Adverse Reactions]*.

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 U/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%), pulmonary embolism (2%), rectal hemorrhage (2%), hemoptysis (2%), deep vein thrombosis (1%), retinal-vein occlusion/thrombosis (1%), polycythemia (1%), transient ischemic attack (1%), and RPLS (<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).

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: February 2012

Reference: 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.

About the Cover
Photo depicts patient undergoing a radical nephrectomy. A recent survey of patient awareness with respect to their options as they face surgery for kidney cancer is covered in this issue. The survey calls attention to the overuse of radical nephrectomy and a lack of awareness by patients with regard to nephron-sparing approaches. (© Copyright, Custom Medical Stock Photo)

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KCJ GUEST EDITOR'S MEMO

Community Oncologists Brace for New Reimbursement Challenges


Christopher G. Wood, MD, FACS

Community oncologists will be facing some tough challenges as reimbursement models begin to change and they are confronted with choices on how to adapt to new contracts and demands. The challenges arise from the quality-based reimbursement models likely to put many community oncologists in a difficult spot. This was the prevailing view coming out of a "town hall" style meeting at this year's meeting of the American Society of Clinical Oncology.

It has been 5 months since the ASCO meeting but the ideas expressed during the Community Oncology Town Hall are still being debated and have provoked a wide range of opinion on what is in store for community oncologists. According to the experts who exchanged ideas during the forum, practices will need to reevaluate their strategies as the fee-for-service reimbursement model is replaced by a new payment system. One of the questions raised was whether community oncologists will invest in the structural changes needed to participate in quality-based reimbursement before they have the contracts that will make the investment worthwhile.

Ultimately, according to one of the other experts at the meeting, "being paid for how much you do will be replaced by being paid for how well you do it." The opportunity to lower costs with various models is proving irresistible for health policy makers. Community oncologists are likely to be squeezed to accept these new models. The up-front costs of making the transition to a new payment system are expected to impose some tough challenges for community oncologists who do not have the economies of scale available to oncologists in institutional and academic settings. For example, even in practices that already have some of the needed infrastructure in place—including sophisticated electronic medical record (EMR) systems, owner-oncologists will need to initiate changes to alter daily processes. How will they allocate their resources and what if their staffs do not immediately adapt to these changes?

By now we have heard a number of times the litany about health care costs as a proportion of gross domestic product (GDP); therein lies much of the impetus for developing new payment models. At the ASCO meeting, evidence was shown that the proportion of the GDP represented by health care costs is 18%, nearly double that of most European countries where quality of care is comparable.

Much remains to be worked out as new payment system begins to take hold. As payers switch from a fee-for-service model to a model that reimburses physicians

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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.

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

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

References

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

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

Argos Announces Globalization of Pivotal Phase 3 ADAPT Study for Personalized Cancer Immunotherapy

DURHAM, NC — Argos Therapeutics Inc., a biopharmaceutical company focused on development and commercialization of fully personalized immunotherapies for the treatment of cancer and infectious diseases using its Arcelis™ technology platform, has expanded its ADAPT Phase 3 clinical study for AGS-003 beyond North America to include sites in Israel, Spain and Czech Republic. To date, more than 80 sites have been activated and more than 100 patients have been screened globally.

"The continued expansion of the ADAPT study to key centers in Europe and Israel demonstrates the increasing excitement and support throughout the international community in advancing cancer immunotherapy research," said Doug Plessinger, VP of Clinical and Medical Affairs of Argos Therapeutics. "This progress ensures we will remain on track to complete enrollment of the trial in the second half of 2014. Furthermore, we expect to activate more European sites in the United Kingdom and Italy, as well as 15-20 more in North America later this year."

The Phase 3 ADAPT clinical study is evaluating AGS-003, an investigational, fully personalized immunotherapy being examined in combination with standard targeted drug therapy to determine its potential to extend the overall survival in newly-diagnosed, unfavorable risk metastatic renal cell carcinoma (mRCC) patients. Secondary endpoints in this study include progression-free survival, safety, overall response and immune response. The ADAPT study is a randomized, multicenter, open-label clinical trial expected to enroll 450 patients in approximately 120 sites, mostly in North America, under an approved Special Protocol Assessment by the Food and Drug Administration.

For more information about AGS-003 and the ADAPT study, visit www.ADAPTkidneycancer.com or follow us on Twitter at @ADAPTkdnycancer.

Metastatic Site Impacts Survival in Targeted RCC Treatment

Bone and liver metastases may have the heaviest impact on the survival of patients receiving targeted therapy for metastatic renal cell carcinoma, suggest data from the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC). The report appeared in medwireNews, a clinical news service of Springer Healthcare Ltd. This is consistent with previous findings in patients treated with cytokines. The current study included 2027 patients who between them received 8 different agents targeting vascular endothelial growth factor (VEGF) and the mammalian target of rapamycin (mTOR).

Overall, 34% of patients had bone metastases and 19% had liver metastases. These impacted on their survival, with median overall survival times of 14.9 vs 25.1 months for patients with and without bone metastases and 14.3 vs 22.2 months for those with and without liver metastases. Both types of metastasis were independent predictors for mortality, with bone metastases raising the risk by 40%, liver metastases by 42%, and the two combined by 82%, relative to metastasis in other sites (primarily the lung). The mortality risk was especially high for patients with multiple bone or liver metastases; their median overall survival time was just 10.1 months. The findings appear in *European Urology*.

Bone and liver metastasis was also associated with IMDC risk group, with bone metastasis affecting 27%, 33%, and 43% of patients in the favorable-, intermediate-, and poor-risk groups, respectively, while liver metastasis was present in 23% of the poor-risk group versus 17% of the favorable- and intermediate-risk groups.

Furthermore, adding bone and liver metastasis to the IMDC predictive model significantly improved its accuracy, report lead researcher Toni Choueiri, MD, (Dana-Farber Cancer Institute, Boston and colleagues in *European Urology*.

NCCN, Pfizer Collaborate on Program Focused on Health Care Quality Improvement and Education

FORT WASHINGTON, PA — The National Comprehensive Cancer Network® (NCCN®) Oncology Research Program (ORP) is collaborating with Pfizer Independent Grants for Learning & Change (IGLC) to establish a peer-reviewed grant program to elicit proposals focused on health care quality improvement and education projects. The NCCN ORP and Pfizer will jointly issue a Request for Proposals (RFP), focused on the development and adoption of evidence-based initiatives to improve patient care and outcomes in renal cell carcinoma and hematologic malignancies.

The intent of the RFP is to encourage academic and community-based organizations to submit proposals describing concepts and ideas for design and implementation of systems or programs that close clinical practice gaps and improve the care of patients with rare cancer types through the establishment of education and support mechanisms for community oncologists. It is expected that grants will fund approximately 9 projects.

"NCCN is pleased to collaborate with Pfizer in this effort," said Joan S. McClure, MS, Senior Vice President, Clinical In-

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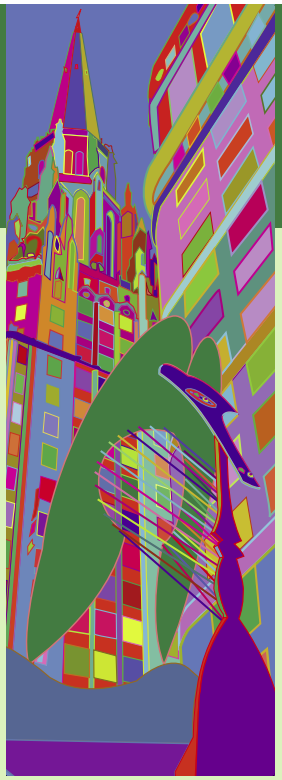

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A New Direction in Immunotherapy: Inhibiting Autophagy Could Promote Long-term Tumor Regression and Limit Toxicity

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An improved understanding of how tumors arise and are treated through immune pathways serves as the basis for what could be a potentially ground-breaking advance in immunotherapy, including the use of high-dose interleukin-2 (IL-2) therapy, still the only strategy offering a cure for renal cell carcinoma. A key consideration is the process of autophagy, a mechanism of programmed cell survival. There appears to be an "autophagic switch" promoting the transition of a tumor into a state where it maintains its viability in a hypoxic, nutrient-limited microenvironment. Recent studies and an important new trial are delineating strategies to inhibit this process and syndrome as part of an exciting effort to achieve longer regressions with immunotherapy.

Autophagy and cancer are interrelated in an intimate fashion. The relationship is complex and seemingly paradoxical with early autophagy limiting tumor initiation but later, promoting cancer growth. New studies have helped to clarify the mechanisms involved and a new perspective on how treatment might be enhanced has emerged in recent years. Although renal cell carcinoma (RCC) is especially insensitive to cytotoxic chemotherapy, it is susceptible to cytolytic effectors of the immune response, including natural killer (NK) cells and T cells. Because the cellular process of autophagy is related to these immune responses and other processes as well, there has been a growing focus on inhibition of autophagy as part of a treatment strategy. One of the key considerations in this line of thinking is whether such inhibition of autophagy might be harnessed with other interventions to more effectively treat RCC with inter- leukin-2 (IL-2). In this sense, further understanding of basic mechanisms of RCC pathogenesis and autophagy could help promote the next generation of pharmacologic modulators of autophagy.

Keywords: autophagy, interleukin-2, apoptosis, HMGB1, NK and T cells, hydroxychloroquine

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Renal Cancer and IL-2 Mechanisms of Efficacy and Resistance

Given the poor response rates of RCC to conventional chemotherapeutic strategies, immunotherapy with IL-2 has long been the focus of investigation and has undergone study in numerous trials to improve efficacy through more sophisticated selection of candidates likely to benefit from it. Immunotherapy with IL-2 induces durable remission, achieving >10 year recurrence free survival in 5-10% of persons with advanced RCC.[1] IL-2 was first described as a T cell growth factor and exerts a broad spectrum of effects on the immune system. The possible mechanisms for its efficacy include the following:

- The augmentation of cytotoxic immune cell functions and reversal of T cell anergy, enabling delivery of immune cells and possibly serum components into tumor.
- IL-2 indirectly limits tumor escape mechanisms such as defective tumor cell expression of Class I or Class II molecules or expansion of regulatory T cells.[1]
- Following systemic administration, IL-2 may also have indirect effects on the tumor microenvironment. IL-2 is associated with dramatic T cell infiltration.
- The IL-2 signaling pathway, its effect on immunity and its effect on various independent mechanisms of tumor surveillance probably play a role, but over the course of 25 years of investigation, researchers have yet to define a clear phenotype of IL-2 responders.[1]

The effect of IL-2 on immunity is related to its pivotal role in determining the magnitude of T cell and NK cell responses, enhancing cytolytic activity and inducing IFN-gamma secretion. This cytokine, first described in 1976, is required for expansion of CD8 + memory T cells during viral infections and as a growth factor that induces class switching in B cells. It helps activate macrophages and maintains lymphoid homeostasis. The precise mechanism by which IL-2 mediates its anticancer effects is still unclear but it is generally thought to be due to its enhanced delivery and activation of cytolytic effectors within tumor sites. Resistance has largely been attributed to effector dysfunction mediated by "exhaustion" [2] or the suppressive influences mediated by regulatory T cells or myeloid-derived suppressor cells.[3,4] An important consid-

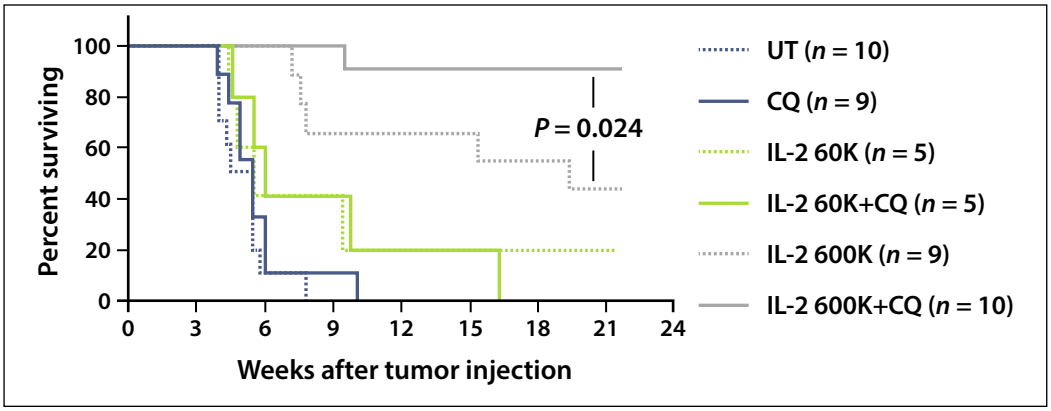

Fig 1 .When compared with the normal saline (untreated control, UT) group, HDIL-2 alone markedly prolonged survival time (P < 0.01). Chloroquine significantly enhanced HDIL-2 antitumor effects (*P* = 0.024).[24]

Table. Combination Chloroquine With HDIL-2 Prolongs Survival Time[24]

Group	n	Survival time, d	Median survival time
PBS	10	27 x 3, 30, 31, 37, 38 x 2,40, 55	31
Chloroquine	9	27, 31, 33, 34, 38 x 2, 42 x 2, 70	38
rIL-2 60K IU	5	31,33,38,66, > 150	38
rIL-2 60K IU + CQ	5	32, 38, 43, 68, 114	43[a]
rIL-2 600K IU	9	50, 53, 55, 107, 135, >150 x 4	135[b]
rIL-2 600K IU + CQ	10	66, >150 x 9	150[b,c]

Abbreviation: CQ, chloroquine
Compare with PBS control group: [a]*P* < 0.05, [b]*P* < 0.001
Compare with rIL-2 600K IU alone: [c]*P* = 0.02

eration is whether the major mechanisms of resistance are related to the target cells' enhanced autophagy and resistance to apoptosis. It appears to be the case and if true, would help explain the lack of response for some individuals to IL-2 immuno-therapy.

Limitations to IL-2 Therapy: Toxicity

The wide range of side effects associated with high-dose IL-2 treatment has proved to be the greatest limitation to its use and has led to numerous studies seeking to identify markers that could be important in predicting response. The side effect issue not only precludes its use in patients who do not meet the pretreatment characteristics of a potential response, the adverse and uncontrollable effects often prevent the continued use of IL-2 in selected patients, even those who have been identified through the use of carboxyanhydrase-9 (CAIX-9) levels. Common side effects include fever, chills, lethargy, diarrhea, nausea/vomiting, anemia thrombocytopenia, eosinophilia, diffuse erythroderma, hepatic dysfunction, and confusion.[5]

The serious side effects of high-dose IL-2 arise from a "capillary leak syndrome," resulting in fluid retention, hypotension, prerenal azotemia, and more serious problems such as adult respiratory distress syndrome and myocardial infarction. There is also an increased risk of infection, especially from gram sensitive bacteria, most likely attributable to a chemotactic defect in neutrophils; prophylactic antibiotics and intravenous fluids may be required.

Autophagy and Counter-regulation With Apoptosis

The two major types of cancer that respond to IL-2 therapy are melanoma and kidney cancer. An intriguing hypothesis is that kidney cancer is more responsive to NK cells. IL-2 promotes both T cell and NK cell induction of immune cell-mediated autophagy in tumor targets. Thus, NK cells and T cells do not merely kill tumor cells, they also induce a state called "programmed cell survival." A study by Michaud et al[6] shed light on this process. This study shows that the process of autophagy ("self-eating"), a form of programmed cell survival[7] is critical to the antitumor immune response elicited by dying tumor cells. Autophagy is one of two mutually antagonistic mechanisms by which cells respond to stress; the other mechanism is apoptosis or programmed cell death.[7,8]

Autophagy is a highly regulated catabolic process involving the degradation of the cell's own components.[9] As tumor cells up-regulate antiapoptotic proteins and lose the function of proapoptotic molecules such as p53, they maintain expression of an abundant proautophagic nuclear protein, high-mobility group box 1(HMGB1), as well as a capacity for enhanced autophagy. Thus, when autophagy-competent tumor cells die, immune clearance mechanisms receive signals to guide later events.[10]

Exploring the relationship between autophagy and apoptosis, our team at the University of Pittsburgh elucidated the complex nature of the association, focusing on the mutual antagonism of these two stress-response pathways.[9] These two pathways share many inducers, and the controlling process reflects a cross-inhibitory interaction with the other. Thus, situations that stimulate apoptosis inhibit autophagy and increased apoptosis inhibits autophagy.

Further elucidation of the role played by autophagy emerged from our review that addresses the notion that autophagy plays two divergent roles.[11] Although au-

(continued on page 77)

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, patients should be managed with dose interruption until symptoms improve
- The use of corticosteroids may be indicated. For grade 4 cases, discontinue AFINITOR. Corticosteroids may be indicated until symptoms resolve
- 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
- 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 respiratory 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
- Be vigilant for signs and symptoms of infection and institute appropriate treatment promptly; interruption or discontinuation of AFINITOR should be considered

Continued on next page

Important Safety Information (cont)

- Discontinue AFINITOR® (everolimus) Tablets if invasive systemic fungal infection is diagnosed and institute appropriate antifungal treatment

Oral Ulceration:

- Mouth ulcers, stomatitis, and oral mucositis have occurred in patients treated with AFINITOR at an incidence ranging from 44% to 86% 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-, 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

Laboratory Tests and Monitoring:

- Elevations of serum creatinine, proteinuria, glucose, lipids, and triglycerides, and reductions of hemoglobin, lymphocytes, neutrophils, and platelets, have been reported
- Renal function (including measurement of blood urea nitrogen, urinary protein, or serum creatinine), blood glucose, lipids, and hematologic parameters should be evaluated prior to treatment and periodically thereafter
- When possible, optimal glucose and lipid control should be achieved before starting a patient on AFINITOR

Drug-Drug Interactions:

- Avoid coadministration with strong CYP3A4 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 and/or PgP inhibitor is required (eg, amprenavir, fosamprenavir, aprepitant, erythromycin, fluconazole, verapamil, diltiazem)
- Avoid coadministration with strong CYP3A4 inducers (eg, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital); however, if coadministration is required, increase the AFINITOR dose from 10 mg daily up to 20 mg daily, using 5-mg increments

Hepatic Impairment:

- Exposure of 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. Women of childbearing potential should be advised to use a highly effective method of 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%). Deaths due to acute respiratory failure (0.7%), infection (0.7%), and acute renal failure (0.4%) were observed on the AFINITOR arm

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 [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; August 2012. **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

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

Brief Summary of Prescribing Information. See full prescribing information for complete product 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

Noninfectious Pneumonitis

Noninfectious pneumonitis is a class effect of rapamycin derivatives, including AFINITOR. Noninfectious 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 noninfectious 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 4 non-infectious pneumonitis, discontinue AFINITOR. Corticosteroids may be indicated until clinical symptoms resolve. 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 Table 1 in Dosage and Administration (2.2) in the full prescribing information]*. If toxicity recurs at grade 3, consider discontinuation of AFINITOR. 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 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 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.

Oral Ulceration

Mouth ulcers, stomatitis, and oral mucositis have occurred in patients treated with AFINITOR at an incidence ranging from 44-86% 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-, 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]*.

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]*.

Laboratory Tests and Monitoring

Renal Function

Elevations of serum creatinine and proteinuria have been reported in clinical trials *[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.

Blood Glucose and Lipids

Hyperglycemia, hyperlipidemia, and hypertriglyceridemia have been reported in clinical trials *[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. 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 clinical trials *[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.

Drug-drug Interactions

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

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

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

Hepatic Impairment

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

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

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

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).

Embryo-fetal Toxicity

There are no adequate and well-controlled studies of AFINITOR in pregnant women; however, 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. Women of childbearing potential should be advised to use a highly effective method of contraception while using AFINITOR and for up to 8 weeks after ending treatment *[see Use in Specific Populations]*.

6 ADVERSE REACTIONS

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

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

Table 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**	

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[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 observed 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

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

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.

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 should not be used *[see Dosage and Administration (2.2, 2.5) in the full prescribing information and Warnings and Precautions]*.

Use caution when AFINITOR is used in combination with moderate CYP3A4 and/or 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]*.

Agents That May Decrease Everolimus Blood Concentrations

CYP3A4 Inducers

In healthy subjects, co-administration of AFINITOR with rifampin, a strong inducer of CYP3A4, decreased everolimus AUC and C_{max} by 63% and 58% respectively, compared to everolimus treatment alone. Consider a dose increase of AFINITOR when co-administered with strong CYP3A4 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]*.

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 two 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

Pregnancy

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

There are no adequate and well-controlled studies of AFINITOR in pregnant women; however, 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, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to use a highly effective method of contraception while receiving AFINITOR and for up to 8 weeks after ending treatment.

In animal reproductive studies, oral administration of everolimus to female rats before mating and through organogenesis induced embryo-fetal toxicities, including increased resorption, pre-implantation and post-implantation loss, decreased numbers of live fetuses, malformation (e.g., sternal cleft), and retarded skeletal development. These effects occurred in the absence of maternal toxicities. Embryo-fetal toxicities 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.

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.

Pediatric Use

Pediatric use of AFINITOR Tablets and AFINITOR DISPERZ is recommended for patients 1 year of age and older with TSC for the treatment of SEGA that requires therapeutic intervention but cannot be curatively resected. The safety and effectiveness of AFINITOR Tablets and AFINITOR DISPERZ have not been established in pediatric patients with renal angiomyolipoma with TSC in the absence of SEGA.

The effectiveness of AFINITOR in pediatric patients with SEGA was demonstrated in two clinical trials based on demonstration of durable objective response, as evidenced by reduction in SEGA tumor volume *[see Clinical Studies (14.5) in the full prescribing information]*. Improvement in disease-related symptoms and overall survival in pediatric patients with SEGA has not been demonstrated. The long term effects of AFINITOR on growth and pubertal development are unknown.

Study 1 was a randomized, double-blind, multicenter trial comparing AFINITOR (n=78) to placebo (n=39) in pediatric and adult patients. The median age was 9.5 years (range 0.8 to 26 years). At the time of randomization, a total of 20 patients were < 3 years of age, 54 patients were 3 to < 12 years of age, 27 patients were 12 to < 18 years of age, and 16 patients were ≥ 18 years of age. The overall nature, type, and frequency of adverse reactions across the age groups evaluated were similar, with the exception of a higher per patient incidence of infectious serious adverse events in patients < 3 years of age. A total of 6 of 13 patients (46%) < 3 years of age had at least one serious adverse event due to infection, compared to 2 of 7 patients (29%) treated with placebo. No patient in any age group discontinued AFINITOR due to infection *[see Adverse Reactions (6.5) in the full prescribing information]*. Subgroup analyses showed reduction in SEGA volume with AFINITOR treatment in all pediatric age subgroups.

Study 2 was an open-label, single-arm, single-center trial of AFINITOR (N=28) in patients aged ≥ 3 years; median age was 11 years (range 3 to 34 years). A total of 16 patients were 3 to < 12 years, 6 patients were 12 to < 18 years, and 6 patients were ≥ 18 years. The frequency of adverse reactions across the age groups was generally similar *[see Adverse Reactions (6.5) in the full prescribing information]*. Subgroup analyses showed reductions in SEGA volume with AFINITOR treatment in all pediatric age subgroups.

Everolimus clearance normalized to body surface area was higher in pediatric patients than in adults with SEGA *[see Clinical Pharmacology (12.3) in the full prescribing information]*. The recommended starting dose and subsequent requirement for therapeutic drug monitoring to achieve and maintain trough concentrations of 5 to 15 ng/mL are the same for adult and pediatric patients with SEGA *[see Dosage and Administration (2.3, 2.4) in the full prescribing information]*.

Geriatric Use

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

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 subjects. In the randomized advanced RCC study, 41% of AFINITOR treated patients were ≥ 65 years of age, while 7% were 75 and over. In the randomized advanced PNET study, 30% of AFINITOR-treated patients were ≥ 65 years of age, while 7% were 75 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]*.

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]*.

Hepatic Impairment

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

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

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

10 OVERDOSAGE

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

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

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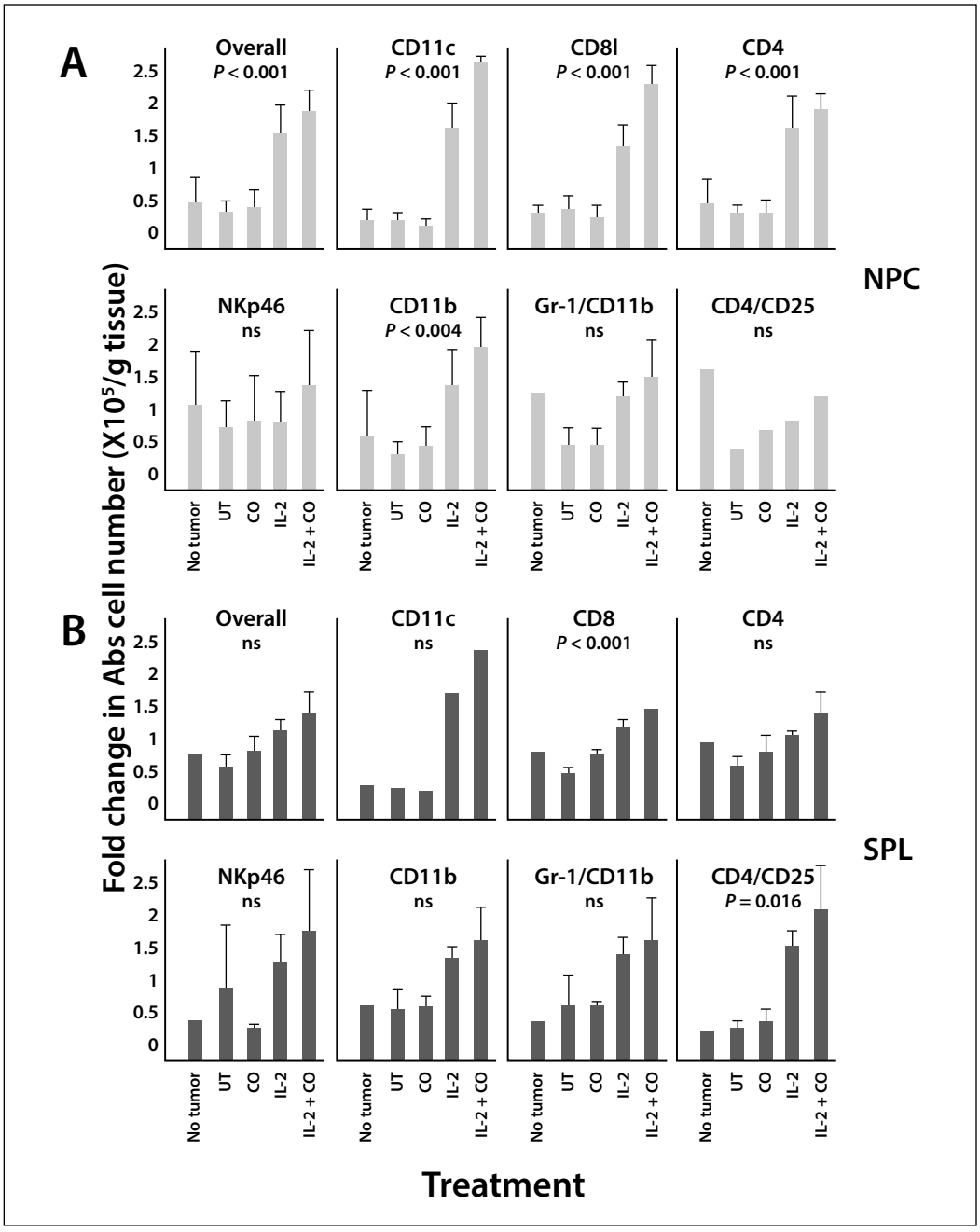

Fig 2. Administration of HDIL-2 and chloroquine (CQ)-stimulated immune cells proliferate and infiltrate into liver and spleen. Mononuclear cells from livers (A) and spleens (3 mice per group; B) were isolated. Cell numbers were counted and normalized by tissue weight. Cells were stained with individual antibodies and analyzed by flow cytometry. Data shown are representative of 1 of 3 similar experiments carried out. ANOVA P values are shown for each set.[24]

tophagy suppresses early tumor formation, many model systems demonstrate that autophagy supports late tumor survival and progression.[7] As is the case in normal cells, autophagy is induced in tumor cells during times of metabolic stress, hypoxia, genomic stress, and ER stress.[12] There is a high correlation between poor prognosis and increased levels of autophagy in a recent study which examined 71 resected adenocarcinomas.[13]

Autophagy thus becomes a factor in tumor cell survival. Many of the current anticancer therapies stress cancer cells—DNA damage through radiation or chemotherapy, deprivation of components necessary for metabolism, inhibition of mitosis, or withdrawal or blockade of growth factor signals. The induction of autophagy provides a survival pathway to circumvent the stress imposed by therapy.[11] Autophagy enables the tumor cell to escape apoptopic cell death. Although the evidence is still preliminary, results from a number of *in vitro* and xenograft preclinical models suggests that pharmacologic inhibition of autophagy sensitizes cancer cells to anticancer therapy.[14-16] This evidence has fueled interest in identifying means to block the process to provide for delivery of more effective antitumor therapy.

Induction of Autophagy by IL-2 Therapy and Activated NK and T Cells

A connection between IL-2 therapy and induction of systemic autophagy has been demonstrated .[17] Autophagy has been implicated in many steps in the immune response, within both T cells and antigen-presenting cells.[18,19] Our studies[20] delineate these associations and demonstrated that human peripheral blood lymphocytes not only provide lytic signals but also promote autophagy in the remaining tumor cells, a process we have referred to as tumor cell 'culling'. At high effector-to-target ratios, autophagy is induced in several human tumors. NK cells are a primary mediator of this process. In addition target cell autophagy was enhanced with administration of IL-2. Immune cell-mediated autophagy (iCMA) promotes cancer cell survival and could represent a target for novel agents.[20]

Autophagy is a mediator of programmed cell survival. It can both suppress tumorigenisis at early stages[21,22] and facilitate a cancer's ability to adapt and recur after therapy in late stages. This has supported the emergent notion that there is an "autophagic switch" arising during carcinogenesis. We don't know fully what the molecular

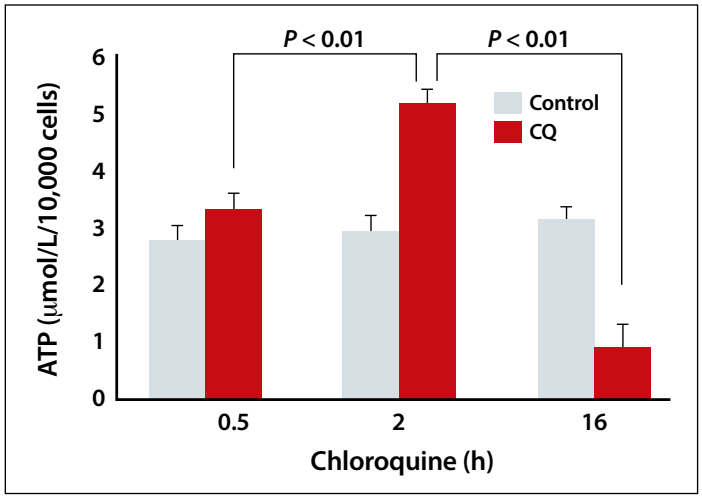

Fig 3. MC38 tumor cells were treated with 100 µmol/L chloroquine for the time indicated. Levels of ATP production were plotted as mean with SDs from experimental replicates, indicating a favorable response.[24]

basis for this switch is but suspect that one of the major receptors for HMGB1, the Receptor for Advanced Glycation Endproducts (RAGE), promotes this process, enhancing autophagy and enabling tumor progression and survival. Our study demonstrated the effect of NK cells on autophagy and showed for the first time that classic cytolytic cells, including NK cells, can often promote survival and autophagy in target cells.[20] We showed that human peripheral blood lymphocytes not only provided lytic signals but also promoted autophagy in the remaining cells. At high effector-to-target ratios, autophagy was induced in several human tumors as assessed by induction of LC3 puncta and diminished p62, classic measures of autophagy.

HMGB1 as an NK-released Cytokine-like Molecule

NK cells also serve another function—to promote the release of a molecule that is highly abundant and spreads in the nucleus of every cell. It is a key component in a chain of communication that enables the immune system to communicate within a damaged tissue. Communication at this level requires an interaction of so-called "danger" signals from infecting agents or from damaged tissues.[5] The signals are facilitated by Pathogen or Damage Associated Molecular Pattern molecules or DAMPS. DAMPs are characterized by the following attributes:

- They are molecules with specific locations and specific roles within cells that usually lack leader secretory sequences.
- They can typically be secreted by myeloid and lymphoid cells and from parenchymal and epithelial cells during stress or during autophagy and subsequent cell death.
- There are important clues as to how these molecules function when one considers a tumor's microenvironment. For example, solid tumors expand and persist for longer periods than normal tissue—reaching a stage where blood vessels cannot proliferate as quickly and a necrotic center develops. With a limited blood supply hypoxia and chronic inflammation are apparent; that promotes angiogenesis, stomagenesis, and epithelial proliferation. This sets the stage for modified systemic and local immune responses or a "wound healing" microenvironment. These conditions are optimal for tumor progression, growth, and metastases. The release of DAMPs from stressed cells is believed to control these changes within the tumor microenvironment.

Further study has focused attention on one of the DAMPs overexpressed in tumor cells—the High Mobility Group Box 1 (HMGB1) protein, a cytokine-like molecule and a nuclear DNA binding protein recently characterized as an extracellular factor involved in the response to infection, injury and inflammation. This molecule has extracellular functions that are cytokine-inducing, che-mokine-like and proangiogenic. The HMGB1 molecule can be released by stressed cells particularly during nonapoptotic death.[5] Cancer cells may have defective apoptotic pathways and as they undergo autophagy and sub- sequent necrotic death the release of DAMPS, such as HMGB1, are increasingly released. This inhibits apoptosis and perpetuates inflammation within the tumor environment.

When HMGB1 is released outside the cell, possibly in response to stress, it acts as a cytokine/inflammatory mediator.[9] Increasing evidence suggests that HMGB1 has important biological functions when transported from the nucleus to the cytoplasm. Increased autophagy can be visualized by fluorescence microscopy or imaging cytometry.[9] HMGB1is indeed a critical regulator of sustained autophagy, and its measure and localization may be our best measure of enhanced autophagy. With autophagy, the cell harbors a turnover mechanism to eliminate damaged organelles, intracellular pathogens and excess cytoplasm. Autophagy promotes catabolic reactions and generates metabolic substrates to meet the energy needs of the cell during periods of stress.[5]

These concepts are beginning to be translated into the clinic and have already had an impact on clinical practice, albeit in a preliminary way. For example, drugs that inhibit HMGB1 cytoplasmic translocation such as ethyl pyruvate (EP) can limit autophagy. EP can suppress liver tumor growth significantly in a dose-dependent manner as we have shown.[5] This is only the beginning of studies to examine the effect of such agents capable of inhibiting autophagy and HMGB1 release and function.

Strategies to Inhibit Autophagy and HMGB1

As various lines of research begin to converge, a clearer picture is emerging of how strategies limiting autophagy could be important targets for therapy. Our studies, for example, showed that target cell autophagy was actually enhanced by IL-2, and cell-to-cell contact strongly enhanced lymphocyte-mediated autophagy. In an ironic

(continued on page 81)

A New Trial Combining IL-2 and Hydroxychloroquine

The main goal of the research study is to determine whether treating renal cell cancer patients with the study drug, hydroxychloroquine, along with IL-2, a standard treatment of kidney cancer that has spread to other parts of the body, can make the cancer easier to kill and eliminate. Another goal is to see how the study drug affects the body's immune cells which fight cancer cells.

Condition	Intervention	Phase
Metastatic Renal Cell Carcinoma	Drug: Hydroxychloroquine Drug: IL-2	Phase 1 Phase 2
Study Type:	Interventional	
Study Design:	Intervention Model: Single Group Assignment Masking: Open Label Primary Purpose: Treatment	
Official Title:	Inhibiting the Systemic Autophagic Syndrome - A Phase I/II Study of Hydroxychloroquine and Aldesleukin in Renal Cell Carcinoma Patients (RCC). A Cytokine Working Group (CWG) Study	

Primary Outcome Measures:

- Proportion of patients with metastatic RCC treated with IL-2 + HCQ at 1200mg/d who experience a clinical complete response. [Time Frame: up to 3 years to accrue and assess outcome] [Designated as safety issue: No]

  Evaluation of target lesions:
  - Complete Response (CR): Disappearance of all target lesions

  Evaluation of non-target lesions:
  - Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level

Secondary Outcome Measures:

- Complete response (CR), overall survival (OS) and time to progression (TTP) of patients with metastatic RCC treated with IL-2 + HCQ to the historical data of patients treated with high dose IL-2 alone in the CWG data base. [Time Frame: up to 3 years to accrue and assess outcome]

  CR (target lesions): Disappearance of all target lesions CR (non-target lesions): Disappearance of all non-target lesions and normalization of tumor marker level

  Survival: date of first protocol treatment to the date of death, or censored at date of last contact.

  TTP: time from the date of first protocol treatment until the date disease progression criteria are met (in responding patients progression criteria uses the reference of the smallest measurements recorded since the treatment started) or is censored at date of last disease assessment for those who have not progressed.

- Safety/toxicity of IL-2 + HCQ compared to CWG database of metastatic RCC patients treated with IL-2 alone: # doses IL-2 during 1st course; toxicity after scheduled 9th dose IL-2; frequency grade III and IV or unexpected or rare toxicities [Time Frame: up to 3 years to accrue and assess outcome] [Designated as safety issue: Yes]

  Number of doses of IL-2 administered during the first course of therapy; toxicity after the scheduled 9th dose of IL-2; frequency of grade III and IV or unexpected or rare toxicities

- Baseline laboratory parameters outlined under "description" (to be correlated with toxicity, response, and survival). [Time Frame: up to 3 years to accrue and assess outcome]

  Baseline laboratory parameters include: miRNAs pre- and post-IL-2; KIR genotyping; T and NK cell enumeration and activation in the peripheral blood; circulating mDC and pDC frequency and DC function, TCR-zeta chain expression in T and NK cells, arginase or arginine levels; circulating cytokines, chemokines, growth factors and angiogenesis mediators

- Known prognostic criteria for RCC patients (Motzer criteria, performance status, prior nephrectomy, presence of liver and/or bone metastases categories) on clinical outcome. [Time Frame: up to 3 years to accrue and assess outcome]

Estimated Enrollment:	39
Study Start Date:	March 2012
Estimated Study Completion Date:	March 2015
Estimated Primary Completion Date:	March 2014 (Final data collection date for primary outcome measure)

Arms	Assigned Intervention Drug:
Experimental: Hydroxychloroquine + IL-2 One course of treatment (84 days) will consist of high dose (600,000 IU/kg) bolus IL-2 administered intravenously every 8 hours on days 1-5 and 15-19 (maximum 14 doses/5 days of administration) and hydroxychloroquine (HCQ) orally started two weeks prior to IL-2 infusions and continued while able to take oral medication for up to 3 courses.	Hydroxychloroquine Continuous oral administration (at 600 mg/d or 1200 mg/d) will be initiated prior to the first dose (day -14) given 14 days prior to initiation of the first dose of IL-2 and then daily or twice a day throughout all three treatment courses. ***Other Name:*** Plaquenil ***Drug:*** IL-2 600,000 IU/kg IV bolus q 8 hrs x days 1-5 and 15-19 (maximum 28 doses - 14 per 5 day cycle) of each 84-day course ***Other Name:*** Aldesleukin

Detailed Description:

The rationale for combining the high dose bolus aldesleukin with hydroxychloroquine includes potential positive interactions on the immune regulatory side, non-overlapping toxicities, and potential for prolongation and increased number of responses based on murine studies conducted at the Univer-

sity of Pittsburgh. This study is a multi-center phase II study designed to estimate the efficacy of combination therapy of standard high dose bolus IL-2 and various doses of hydroxychloroquine therapy in metastatic RCC patients.

Eligibility

Ages Eligible for Study:	18 Years and older
Genders Eligible for Study:	Both
Accepts Healthy Volunteers:	No Criteria

Inclusion Criteria:

- Histologically confirmed metastatic renal cell carcinoma with predominantly clear cell histology.
- Have measurable disease by RECIST 1.1 criteria. For example, this would include tumor in the lung, liver, and retroperitoneum. Bone disease is difficult to follow and quantify and as a sole site would not be acceptable.
- Patients must be at least 4 weeks from radiation or surgery and recovered from all ill effects.
- Age ≥18 years.
- Karnofsky Performance Status ≥80%.
- Adequate end organ function:
  1. Hematologic: ANC ≥ 1000cells/uL, platelets ≥ 100,000/uL, hemoglobin ≥ 9g/dl (pre transfusion values used for prognostic factor, can be transfused or use recombinant erythropoietin growth factors but must not have active bleeding).
  2. Liver: AST ≤ 2 x ULN (upper limit of normal), serum total bilirubin ≤ 2 x ULN (except for patients with Gilbert's Syndrome).
  3. Renal: serum creatinine ≤ 1.5 mg/dL or estimated creatinine clearance ≥ 60ml/min using Cockcroft-Gault estimation using the formula per protocol.
  4. Pulmonary: FEV1 ≥ 2.0 liters or ≥ 75% of predicted for height and age. (PFTs are required for patients over 50 or with significant pulmonary or smoking history defined as >20 pack years or history of COPD/emphysema).
  5. Cardiac: No evidence of congestive heart failure, symptoms of coronary artery disease, myocardial infarction less than one year prior to entry, serious cardiac arrhythmias, or unstable angina. Patients who are over 40 or have had previous cardiac disease will be required to have a negative or low probability cardiac stress test for cardiac ischemia.
- Women should not be lactating and, if of childbearing age, have a negative pregnancy test within two weeks of entry to the study.
- Appropriate contraception in both genders.
- The patient must be competent and have signed informed consent.
- CNS: No history of cerebrovascular accident, transient ischemic attacks, central nervous system or brain metastases.

Exclusion Criteria:

- Patients who have received prior systemic therapy for metastatic RCC or have previously received IL-2 are not eligible. Patients on HCQ in neoadjuvant protocols or in the past for clinical indications ARE eligible.
- Concomitant second malignancy except for non-melanoma skin cancer, and non-invasive cancer such as cervical CIS, superficial bladder cancer without local recurrence or breast CIS.
- In patients with a prior history of invasive malignancy, less than five years in complete remission.
- Positive serology for HIV, hepatitis B or hepatitis C.
- Significant co-morbid illness such as uncontrolled diabetes or active infection that would preclude treatment on this regimen.
- Use of corticosteroids or other immunosuppression (if patient had been taking steroids, at least 2 weeks must have passed since the last dose).
- History of inflammatory bowel disease or other serious autoimmune disease. (Not including thyroiditis and rheumatoid arthritis). Patients already on hydroxychloroquine for such disorders are not eligible.
- Patients with organ allografts.
- Uncontrolled hypertension (BP >150/100 mmHg).
- Proteinuria dipstick > 3+ or ≥ 2gm/24 hours.
- Urine protein:creatinine ratio ≥ 1.0 at screening.
- Major surgery, open biopsy, significant traumatic injury within 28 days of starting treatment or anticipation of need for major surgical procedure during the course of the study.
- Minor surgical procedures, fine needle aspirations or core biopsies within 7 days prior to starting treatment. Central venous catheter placements are permitted.
- History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 6 months prior to starting treatment.
- Serious, non-healing wound, ulcer, or bone fracture.
- History of tumor-related or other serious hemorrhage, bleeding diathesis, or underlying coagulopathy.
- History of deep venous thrombosis, clinically significant peripheral vascular disease, or other thrombotic event.
- Inability to comply with study and/or follow-up procedures.
- Individuals with known history of glucose 6 phosphate deficiency are excluded from the trial (possible issue with HCQ tolerance).
- Patients with previously documented macular degeneration or diabetic retinopathy are excluded from the trial.
- Baseline EKG with QTc > 470 msec (including subjects on medication). Subjects with ventricular pacemaker for whom QT interval is not measurable will be eligible on a case-by-case basis.

Contacts and Locations

Please refer to this study by its ClinicalTrials.gov identifier: NCT01550367

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twist, cell-mediated autophagy promotes resistance from treatments designed to eradicate tumor cells, and this may be generalizably true for chemotherapy and radiation therapy as well. In view of this lymphocyte-induced cell-mediated autophagy and its promotion of cancer cell survival, we need a more nuanced approach to the use of IL-2. Ongoing clinical trials are exploring such approaches and generating wide interest, and an improved understanding about the use of IL-2 in that setting has emerged.

Although IL-2 therapy can be potentially curative, it creates a systemic autophagic syndrome, limiting vital processes within tissues at the expense of enhanced cell survival .[2,3] While limited or localized tissue dysfunction preoccupied with the process of autophagy is not a problem, complete involvement of the organ in the autophagic process, now excessive, limits the ability of that tissue to perform its primary function, such as respiration for the lung or bile secretion for the liver. Our pivotal Cytokine Working Group study pursuing this more nuanced strategy for IL-2 immunotherapy proposes that the autophagy inhibitor hydroxychloroquine would enhance the effect of IL-2 and limit toxicity. Chloroquine has been used for many years as an antimalarial but it also inhibits autophagy by blocking acidification of the lysosome, preventing fusion with the autophagosome.[23] Previous studies reported that the parent molecule, chloroquine demonstrates significant antitumor activity by inhibiting the induction of autophagy following cancer therapy. In a mouse liver tumor model, we compared the use of high-dose IL-2 with chloroquine with IL-2 alone (**Figure 1**).[24] The study produced some important results:

- The combination of IL-2 with chloroquine increased long term survival, decreased toxicity associated with vascular leakage (**Table 1**), and enhanced immune cell proliferation and infiltration in the liver and spleen.
- Immunofluorescent staining in liver tissue showed that the combination prevented HMBG1 translocation. The combination treatment significantly decreased HMBG1 compared with high-dose IL-2 alone. Its effect on other parameters is also shown in **Figures 2** and **3**.
- High-dose IL-2 administration induced profound mitochondrial changes and heightened autophagy.
- Chloroquine treatment induced tumor cell apoptosis.

Current clinical studies of autophagy inhibition in RCC

Armed with the knowledge of the animal study inhibiting autophagy with the combination of high-dose IL-2 and chloroquine, we have initiated a clinical study to evaluate the delivery of this therapy in patients with advanced renal cancer. *(See related trial information from the website clinicaltrials.gov.)* This study, with its protocol opened up at 5 major centers, has opened a new avenue of research and constitute a major advance in the administration of IL-2 in kidney cancer and melanoma. Its application may also be important in other emergent immunotherapies such as those targeting CTLA-4 and PD1, associated with 'metastatic immunity' at normal tissue sites,[25-27] in part related to HMGB1 and enhanced autophagy.

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Neoadjuvant Systemic Therapy in Locally Advanced Renal Cell Carcinoma: Pro and Con

Summary: Clearly the jury is still out regarding the utility of neoadjuvant systemic targeted therapy for locally advanced kidney cancer prior to extirpative surgery. Both authors make good points regarding the potential utility, and the potential downsides to such an approach. Truly unresectable primary tumors, in my experience, are as rare as hen's teeth, but the possibility of altering the operative approach, from open to laparoscopic or from radical to partial, remains enticing. Clearly, the first generation of targeted agents, such as sunitinib and sorafenib, have fallen well short of the mark regarding meaningful primary tumor response, but some of the "next generation" agents such as axitinib and others may hold more promise. Concerns about wound complications and residual disease rebound due to elevated VEGF levels notwithstanding, the neoadjuvant approach in locally advanced and advanced kidney cancer is the next great research frontier in the management of patients. Time, and carefully crafted clinical research studies, will demonstrate whether or not it will be a treatment advance in the management of our patients.
Christopher G. Wood, MD, Guest Editor

The Pro Argument

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To improve our current treatment paradigms for patients with renal cell cancer (RCC), it is critical that we investigate the potential benefits of neoadjuvant therapy, especially for patients with large or locally advanced primary tumors. A key advantage of pre-surgical therapy is the ability to shrink tumors and reduce the morbidity of surgery by facilitating minimally invasive approaches or by allowing less radical procedures. In addition, neoadjuvant therapy allows for treatment of subclinical metastatic disease while it is microscopic and may potentially decrease recurrence rates. Finally, pre-surgical therapy allows for the study of tissue endpoints in surgical specimens after treatment, which improves our understanding of RCC biology and may lead to improvements in future systemic therapies. Although the current data provide minimal evidence for routine neoadjuvant therapy in our current practice, it remains crucial that neoadjuvant paradigms be investigated through clinical trials in order to continue to maximize the potential benefits of newer therapies.

Patients with non-metastatic locally advanced renal cell carcinoma have primary tumors, which are usually large and may invade the perinephric fat, venous system or adjacent structures but otherwise have no evidence of metastatic disease.

Patients with unresectable tumors. When RCC tumors invade the structures adjacent to the kidney, surgery becomes more complex because excision of all or part of the surrounding organs can become necessary to completely remove all known tumor. Surgery can include resection of the spleen, stomach, diaphragm, pancreas, liver, blood vessels, or bowels. In some cases, the risk of surgical resection becomes prohibitive and tumors are defined as "unresectable". However, this definition varies considerably among surgeons, and there no uniformly accepted criteria for unresectable tumors. This lack of an accepted definition for unresectable tumors stems from the immunotherapy era, when there was very little hope for response from systemic therapy in primary tumors[1,2] and surgeons had few options for RCC invading adjacent organs. For non-metastatic tumors invading adjacent organs, survival was similar to metastatic RCC, and aggressive complete surgical resection was associated with better outcomes.[3]

In the early targeted therapy era, several case reports and small series showed that meaningful primary tumor responses were possible using newer targeted agents.[4] However, a large retrospective review of 162 metastatic RCC patients treated with targeted agents and the primary tumor in place, demonstrated that large meaningful primary tumor responses were rare, but minor primary tumor responses were seen in many patients.[5] Most surgeons would agree that tumor shrinkage of 50% of the diameter, could make the majority of unresectable tumors amenable to surgery, but it is unclear if a 1 cm decrease in tumor diameter improves surgical outcomes in patients who have tumors judged unresectable.

Phase 2 trials or retrospective series of patients with "unresectable" tumors have been published with modestly encouraging results. In a retrospective series of ten patients with unresectable primary tumor treated with sunitinib, the authors report 14% median response in the primary tumor with 3 patients being reconsidered for surgery after neoadjuvant treatment.[6] Investigators at the Cleveland Clinic evaluated 19 patients with locally advanced or metastatic disease deemed unsuitable for initial nephrectomy after treatment with a median of 2 cycles of sunitinib. Partial responses in the primary tumor (30% shrinkage) were demonstrated in three patients (16%) and four patients (21%) eventually had surgery.[7]

(continued on page 90)

GlaxoSmithKline
Oncology

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)

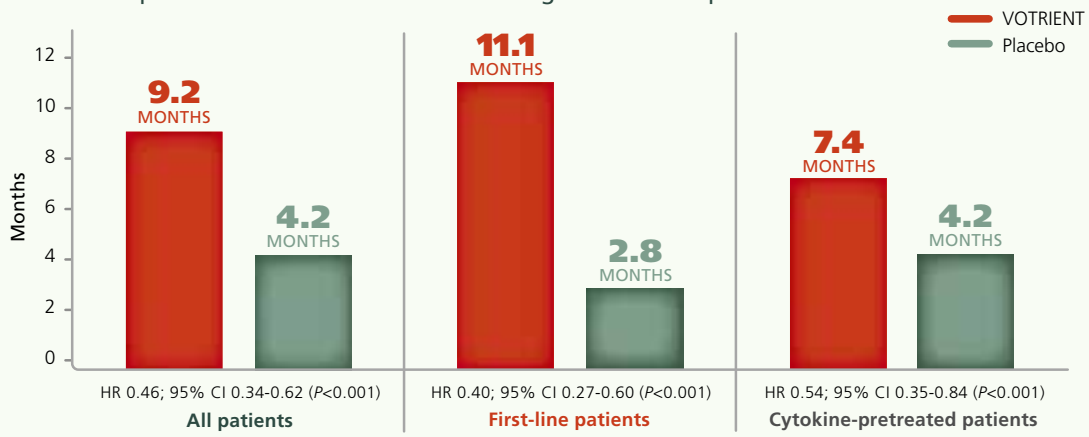
EFFICACY LIGHTS THE WAY

GlaxoSmithKline Oncology

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
- The dosage of VOTRIENT in patients with moderate hepatic impairment 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 Section 2.2 of accompanying Brief Summary

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.

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

- **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.1.2013. ©National Comprehensive Cancer Network, Inc. 2013. All rights reserved. Accessed February 1, 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.

Votrient®
pazopanib tablets (200 mg)

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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 receive d 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%).

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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In 2011, the same authors updated their findings with a phase 2 trial of 30 patients with unresectable tumors who were given sunitinib with their primary tumor in situ, and reported a median change in primary tumors of -22% corresponding to a median decrease of 1.2 cm.[8] Thirteen patients (45%) were subsequently able to undergo nephrectomy, which was the primary endpoint of the study. Given this data, some surgeons would argue against neoadjuvant therapy for most patients because primary tumor size reduction is minimal. However, in this patient population facing otherwise extensive surgery, it is important to consider that in some trials up to 28% achieved a partial response[9] and very few patients from any series had significant increase in tumor size while on targeted therapy. Clearly, the best rationale for using available targeted agents in a neoadjuvant approach can be made for patients with adjacent organ involvement considering that even modest tumor shrinkage may potentially decrease the extent of surgery for patients with historically poor outcomes.

Patients with upper level tumor thrombus. In patients with inferior vena cava (IVC) tumor thrombus, surgery becomes increasingly difficult when the thrombus extends into the upper IVC or right heart circulation. When tumor thrombus is down staged using neoadjuvant therapy, patients may benefit by avoiding sternotomy or cardiopulmonary bypass, which may be used to excise upper level IVC thrombus. Early reports using targeted therapy demonstrated the feasibility of the neoadjuvant approach to shrink tumor thrombus.[10] However, larger series have shown that only a small minority of patients demonstrated significant decrease in thrombus height, while a larger proportion of patients had an increase in thrombus height while on targeted therapy.[11] While neoadjuvant therapy could clearly have significant benefits for patients with upper level IVC thrombus, there is a substantial risk of cardiac or hepatic failure when tumor thrombus propagates in the IVC. As a result, few surgeons currently advocate standard neoadjuvant therapy for patients with upper level IVC thrombus. Future neoadjuvant clinical trials should evaluate this patient population using newer systemic therapies, as the potential for benefit would be increased, if reliable and significant responses within the tumor thrombus are able to be achieved.

Facilitating less extensive surgery. In patients with large primary tumors, neoadjuvant therapy may decrease the size of primary tumors, enabling less extensive surgery or surgery using minimally invasive techniques. Neoadjuvant targeted therapy clinical trials have included patients treated with minimally invasive approaches for nephrectomy but not studied the ability to perform less invasive surgery as an outcome.[9,12] Several studies have also suggested that neoadjuvant approach may enable partial nephrectomy in some patients, although no study has addressed this question as a primary outcome.

A multicenter review of 14 partial nephrectomies in patients treated with targeted therapy demonstrated the feasibility of this using targeted therapy before partial nephrectomy.[13] A recent phase two trial of 24 non-metastatic patients presented at the ASCO annual meeting included five patients who were treated with partial nephrectomy after receiving neoadjuvant axitinib.[9] However, the influence of systemic therapy on the ability to perform partial nephrectomy was not assessed as an outcome. If future neoadjuvant studies are able to demonstrate an increased ability to perform nephron sparing surgery, this approach would likely benefit many patients, given the deleterious effects of renal failure on mortality.[14] However, it is imperative that randomized clinical trials are conducted to address the best role of neoadjuvant systemic therapy in patients without metastatic disease for whom surgery may be curable, prior to changing the treatment paradigm. Future studies should focus on critically analyzing the risks and benefits of neoadjuvant therapy for specific patient populations, with attention to how non-metastatic RCC patients tolerate the adverse events associated with systemic therapy.

Treatment of subclinical metastatic disease. Despite aggressive surgical resection, half of the patients with locally advanced RCC will ultimately progress to metastatic RCC. To improve outcomes in these high risk patients, it is imperative that a systemic approach is utilized because distant metastases develop from microscopic metastatic disease which was present at the time of surgery. Over the last decade, the development of molecular agents which target angiogenesis and cell survival pathways has revolutionized the treatment of metastatic RCC with improved response rates and longer survival. However, evidence suggests that these agents work most directly on endothelial and stromal cells within the tumor and do not induce cell death at physiologic concentrations, which possibly limits their effective use as neoadjuvant agents.

Neoadjuvant therapy has demonstrated survival advantages and become standard for several types of locally advanced cancers. However, to date, no adjuvant or neoadjuvant therapy has demonstrated a benefit in survival or recurrence rates for patients with high risk RCC. With new attention being focused on individualized immunotherapy among other immunotherapeutic approaches for metastatic RCC, there will be new opportunities to evaluate these agents in neoadjuvant and adjuvant settings.

Evaluation of tissue endpoints. The scientific value of studying tumors after systemic treatment must be considered as a benefit to the neoadjuvant approach with systemic therapies. Despite improvements in overall survival over the last 2 decades, the prognosis for most patients with for metastatic RCC remains dismal. To improve care for all patients, we must investigate new types of treatment and understand how resistance develops with current therapies. With a lack of quality animal models to study RCC, it is important that we closely examine tissue before and after systemic therapy to gain insights into RCC cancer biology. Given the multiple pathways which are activated or inhibited by targeted agents, it will become increasingly important to closely compare what we expect from preclinical studies to actual patient samples to allow for personalized therapeutic approaches.

In conclusion, neoadjuvant therapy for RCC has more potential advantages than proven benefit. Targeted therapies have undoubtedly improved the treatment of metastatic RCC

with high initial response rates, but the median overall survival in mRCC has remained poor. Locally advanced RCC clearly represent a high risk for progression to metastatic disease, and future neoadjuvant clinical trials in this patient population will continue to be an excellent opportunity to impact the overall treatment of patients with RCC.

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The Con Argument

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The introduction of targeted therapy over the past decade marked a major breakthrough in the management of patients with metastatic renal cell carcinoma (RCC). Multiple studies have demonstrated extended survival and less toxicity with targeted therapeutics when compared to immunotherapy.[1-5] Despite the impact of the integration of surgery with targeted therapeutics on the improvement of outcomes for patients with metastatic RCC, surgery should remain the gold standard for patients without metastatic disease secondary to its potential to rid the patient of disease and, more importantly, by the fact that, unlike interleukin-2, there is no curative potential with the currently available targeted agents.

In order to be justified, the routine use of systemic therapy prior to surgery for locally advanced disease should serve at least one of two purposes: To treat micrometastatic disease likely present based on the high risk nature of the primary tumor or to clinically downstage the primary tumor in order to make it more easily resected and cause less morbidity for the patient. The use of platinum-based combination chemotherapy prior to radical cystectomy in patients with muscle-invasive bladder cancer is based on level 1 evidence demonstrating a survival benefit not only overall but most pronounced in patients with higher risk (eg, $\geq T_3$) disease.[6] The morbidity of radical cystectomy requires a long recovery period and therefore it makes sense to treat a patient systemically prior to surgery when they are most apt to handle the toxicity associated with chemotherapy. This is not to say that surgery for locally advanced RCC is any less morbid. However, unlike cisplatin-based chemotherapy, targeted therapy is not cytotoxic and therefore will not realistically treat any unseen micrometastatic disease.

Significant regression of the primary tumor is the exception, not the rule. Although there are a few case reports showing dramatic responses in the primary tumor with targeted therapy, most studies have demonstrated significant variability in response based on the initial tumor size and the targeted agent used. In addition, a greater response is more likely to be noted in metastatic lesions rather than the primary tumor and this may be based on the biology of the disease.[7, 8] In a large retrospective study examining 168 patients with metastatic RCC and their primary tumor *in situ*, Abel *et al.* showed that the median overall change in maximum primary tumor diameter was only a 7.1 percent decrease with a median time to reach this of 62 days.[9] Furthermore, of the entire cohort, only 6 percent of patients had a partial response (>30 percent decrease) based on Response Evaluation Criteria in Solid Tumors (RECIST) criteria. In addition, other studies examining the effect of targeted therapy on primary tumor size demonstrate that, although progression is rare during the treatment period, the majority of patients show stable disease and very few (< 10 percent) exhibit tumor shrinkage consistent with a partial response by RECIST criteria.[10, 11] What is interesting from these studies is that in the majority patients who had a response in the primary tumor, the absolute decrease in primary tumor size was less than 2 centimeters, a finding not likely to have affected complete surgical resection in the absence of neoadjuvant treatment.

Neoadjuvant targeted therapy has been advocated for patients with thrombus within the inferior vena cava (IVC). In theory, based on isolated case reports, pre-surgical treatment with targeted therapy could decrease the level of the thrombus thereby facilitating a less morbid operation (e.g., no ster-

notomy or cardiopulmonary bypass) and improving outcome. However, in a retrospective multi-institutional review of patients undergoing targeted therapy treatment prior to nephrectomy and IVC thrombectomy, Cost *et al.* found that only a small percentage of patients demonstrated a decrease in height of the thrombus and, in fact, the thrombus height increased in a significant number of patients while they were being treated with targeted therapy.[12] Importantly, there was only a single patient, whose thrombus went from a level IV to level III, where the surgical method was potentially altered. Therefore, at present, it is reasonable to state that a patient with RCC and an IVC thrombus would be best served through immediate resection by an experienced team of surgeons and not be delayed with targeted therapy treatment with likely little benefit.

Resectability is in the eye of the surgeon. There is no doubt that RCC can invade adjacent organs such as the liver, spleen, bowel, pancreas, and diaphragm and this increases not only the morbidity of the surgery but the chance for a poorer outcome. Nonetheless, the definition of unresectable varies widely depending on the institution and the surgeon. Although survival of patients with clinical T4 disease is poor, aggressive surgical resection can be associated with improved outcomes.[13] The question though is whether or not neoadjuvant targeted therapy could facilitate surgery on unresectable tumors. A recent study by Rini *et al.* evaluated 30 patients (19 with metastatic RCC and 11 without) whose primary tumors were deemed unresectable. These patients underwent treatment with sunitinib (median of four cycles) and 13 (45%) were able to proceed with nephrectomy. Overall, there was a median change of 22 percent decrease in primary tumors from the entire cohort and this was related to median reduction of 1.2 cm. This, in combination with the fact that 9 of the 13 patients (or 69.2%) able to undergo resection actually underwent a partial nephrectomy, should highlight how unresectable these tumors were in the first place.

The benefit of neoadjuvant therapy should outweigh its morbidity. Although the toxicity profile of targeted agents is better when compared to immunotherapy or systemic chemotherapy, targeted therapy is not without its own side effects.[14] In general, VEGF inhibitors have been associated with an increased risk of hypertension, thyroid dysfunction, and more rarely renal dysfunction and cardiotoxicity, the latter leading to a decrease in left ventricular ejection fraction. There is also a small but real increased risk of arterial thromboembolic events. Less serious but nonetheless bothersome side effects associated with VEGF inhibitors include fatigue, diarrhea, skeletal muscle wasting, and the very common hand-foot syndrome. Although serious side effects with mTOR inhibitors are rare, these drugs can be associated with anemia, nausea, rash, hyperglycemia, hyperlipidemia and asthenia. The most serious complication of treatment with mTOR inhibitors is drug-induced pneumonitis which can be fatal. Although baseline co-morbidities can help predict the likelihood of complications in patients treated with neoadjuvant targeted therapy, even healthy patients are at risk for potential morbidity which may delay or even preclude curative surgical resection. In addition, although retrospective studies have shown that severe peri-operative complications are rare, patients undergoing neoadjuvant treatment with targeted therapy were more likely to experience wound healing issues during the peri-operative period, an element likely due to the mechanistic action of the drug in hindering angiogenesis.[15, 16]

Finally, valid arguments against routine neoadjuvant systemic therapy in patients with locally advanced RCC are that there could be a progression of disease during therapy (as up to one third of metastatic patients are known to progress on single-agent therapy) and, importantly, there could be an adverse change to the basic tumor biology upon introducing a targeted agent.[17] Studies have shown that VEGF inhibitors, although eliciting anti-tumor effects, simultaneously produce adaptive changes in the tumor resulting in more aggressive behavior and increased progression.[18, 19] In fact, in our own laboratory, we have noted increased activation of pro-survival cellular signaling pathways within the tumor upon treatment of mice with either a VEGF or mTOR inhibitor, indicating that pro-survival networks are at play even before there is a phenotypic change in tumor growth. These data would indicate that, at least in a subset of patients, neoadjuvant targeted therapy treatment could have an undesirable effect on the primary tumor putting them at a higher risk of disease progression.

In conclusion, based on the current regimen of targeted agents, there is no justifiable reason for the use of systemic targeted therapy prior to surgery for locally advanced RCC. Upfront surgery should remain the standard of care and patients should be treated in a timely manner by an experienced surgeon at a high-volume institution to decrease morbidity and improve outcome.

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GUEST EDITOR'S MEMO *(continued from page 66)*

based on how they can demonstrate quality of care, community oncologists will be dividing their time between two worlds: it may be necessary to track both services performed and quality-of-care measurements so that each can be provided for reimbursement to different payers. Is this bad? Not necessarily, according to opinion expressed during the ASCO conference. Patients will likely benefit and clinicians can expect to gain more by demonstrating they are providing a high level of quality care. Our continued involvement as stakeholders in the evolving health care marketplace is important as new systems challenge oncologists' ability to cope with the transition.

Christopher G. Wood, MD, FACS
Guest Editor

Survey Warns Physicians About Overuse of Radical Nephrectomy and Relationship Between Kidney Cancer and Chronic Kidney Disease

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The "take-home" message from recently published findings on patient and physician awareness is clear: physicians need to clarify surgical options available to their patients and delineate the advantages of partial nephrectomy over radical nephrectomy. Educational initiatives for surgeons and patients alike are required to promote the benefits of kidney-sparing approaches when possible and reduce use of radical nephrectomy when it is not necessary.

Despite an abundance of evidence supporting the expanded use of nephron-sparing surgery in a new pool of patients who would be eligible for such management, patients often lack the awareness or the knowledge to choose among the options available to them. The educational gap—at both the patient and physician level is largely responsible for the continued use of radical nephrectomy and an increased risk for chronic kidney disease (CKD).

Results of a national survey commissioned by the National Kidney Foundation [1] uncovered some disturbing results about a knowledge deficit involving a broad spectrum of issues in this setting, including a lack of awareness as this initiative assessed the educational needs of the kidney cancer community. Among the key findings:

- Patients tended to be unaware that kidney cancer and radical nephrectomy are risk factors for CKD.
- Only a minority of patients underwent partial nephrectomy or were given it as an option for their early-stage kidney cancer.
- Findings from the survey suggest a knowledge deficit among physicians, surgeons, patients and caregivers alike that there is a bidirectional relationship between kidney cancer and CKD and that kidney-sparing surgery is preferable when feasible.

Keywords: radical nephrectomy, partial nephrectomy, nephron-sparing surgery, survey, chronic kidney disease (CKD), National Kidney Foundation

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The survey addressed many factors related to the care of patients with renal cell carcinoma, including the role of caregivers, the nature of information resources used, and health maintenance strategies used by patients with a solitary kidney. But the focus of our report, generated from the data gathered in the NKF survey was specific—targeting patient and caregiver knowledge about surgical options for management of RCC and its impact on overall kidney health.

The reason for this focus arises from another trend observed in recent years. Despite a growing body of evidence in support of nephron-sparing surgery, radical nephrectomy is still grossly overused in the management of small masses. The overuse of radical nephrectomy is apparent despite evidence indicating that kidney-sparing surgery is a sound strategy providing oncologic control equivalent to radical nephrectomy while preserving kidney function and preventing CKD.

During the last decade, well-done clinical studies have fortified the case for partial nephrectomy when possible based on 3 essential points.[2-6]

(1) The pathology of resected renal tumors indicates that up to 20% are completely benign (angiomyolipoma, renal oncocytoma, and metanephric adenoma) with no metastatic potential; 25% are indolent cancers (papillary and chromophobe) with limited metastatic potential, and for the majority of T1 cancers that are the more malignant conventional clear cell carcinoma (54%), long-term cancer-specific survival rates after resection are ≥90%.[7] (**Table 1**)

(2) Oncologic results for patients with T1 tumors are equivalent whether partial or radical nephrectomy is done.

(3) CKD is a pre-existing condition in approximately 26% of patients with a normal serum creatinine level prior to surgical resection. Because radical nephrectomy is a risk factor for CKD or the worsening of pre-existing CKD, the casual use of radical nephrectomy for a small renal mass is a potentially toxic event.[2]

Table 1. Characteristics of Tumor at Diagnosis

	Percentage of Respondents
Size of tumor at diagnosis	
4 cm	15
4-7 cm	30
7 cm	22
Don't know or were not told	33
Type of tumor at diagnosis	
Benign	11
Indolent with limited metastatic potential	27
Clear cell	7
Don't know or were not told	55

Note: N=417

Table 2. Patient Surgical History

	Percentage of Respondents
Type of surgery	
Radical nephrectomy	67
Radical nephrectomy (laparoscopic)	19
Partial nephrectomy	18
Surgery for removal of metastases	6
Respondent does not remember type of surgery	3
Time of surgery	
1 y ago	20
1-3 y ago	32
3 y ago	48
Physician discussed candidacy for partial nephrectomy	
Yes, but still recommended radicalnephrectomy	38
No	25
Yes, but was told patient not a candidate	24
Respondent does not remember if discussed	8
Respondent does not understand the differences in surgeries enough to comment	5

Note: N=363. Total response rate is 113% due to multiple responses

The obvious question raised by these points is why have they not had a significant impact on the decision to use radical nephrectomy routinely when a partial nephrectomy can achieve a similar results with less risk? The findings of the survey are also disturbing in view of epidemiological trends showing a change in the profile of the patient with kidney tumor. Greater use of cross-sectional imaging techniques during the last 20 years typically ordered to assess nonspecific abdominal or musculoskeletal symptoms or during unrelated cancer care has detected more asymptomatic small masses. Approximately 70% of surgically resected kidney tumors are spotted incidentally, with a median tumor size of <4 cm.[8] Consequently, there is a new pool of patients with small renal masses (T1, <7 cm). They have a generally favorable prognosis after surgical resection by either radical or partial nephrectomy.

Despite these trends—the growing awareness that partial and radical nephrectomy provide virtually equivalent outcomes for small renal masses—radical nephrectomy remains grossly overused in the US.[9] As the survey points, many urologists still have misconceptions about the need for radical nephrectomy, and this attitude is reflected in evidence from national databases, such as the National Inpatient Sample, Surveillance Epidemiology and End Results (SEER) database and the SEER database linked to Medicare claims. Data from these sources indicate that approximately 70% to 80% of patients with tumors <4 cm still undergo radical nephrectomy.[10-13]

One of the reasons for the inclination to use radical nephrectomy is that urologists often believe a "quick" radical nephrectomy in an elderly patient would result in the patient's being exposed to fewer postoperative complications than he or she would with a partial nephrectomy. It is a misconception. This subset of patients would benefit the most from kidney preservation. Little if any justification for the approach of a radical nephrectomy is evident in the literature for this group. For example, a Memorial Sloan Kettering Cancer Center study assessed age and type of procedure; statistical evidence was lacking for a risk of complications associated with partial nephrectomy increasing with advancing age. The investigators concluded such elderly patients should be eligible for partial nephrectomy because of the nephron sparing advantage gained with partial nephrectomy. [14]

The Study

Details of the study, including methodology, patient characteristics, the extent of their awareness of surgical options, and physician responses provide an accurate snapshot of the interplay of factors surrounding the decision to use radical vs partial nephrectomy (**Table 2**). And the lack of knowledge—for both patients and in many cases physicians—was surprising.

Survey participants

There were a total of 417 respondents (365 patients and 52 caregivers). Caregivers answered the same questions as patients but in a format that made reference to the patient they cared for.[1] Patients had an average age of 60 years and caregivers 53 years. Of the patients: 43% had early-stage cancer, 30% had late-stage cancer, and 27% did not know their stage. Radical nephrectomy was the predominant surgical treatment for each group: about 83% in the early stage, 92% in late stage, and 86% in the don't know group. More than half the respondents did not remember or were not told what type of kidney tumor they or their patient had and 33% did not know or were not told how large the tumor was.

Surgical treatment

Among patients who underwent radical nephrectomy, 25% said they were not aware of the option of partial

Table 3. Participant Knowledge Regarding Kidney Cancer and CKD[1]

	Percentage of Participants with Knowledge
Risk factor for CKD	
Loss of a kidney due to an injury or a disease other than cancer	40
Radical nephrectomy for cancer treatment	62
Medications that cause kidney damage	68
High blood pressure	66
Diabetes	66
Family history of kidney disease	60
Older than 60 y	52
Having urinary obstructions	49
Repeated urinary infections	45
Heart and blood vessel disease	42
Racial/ethnic background that is African American, Hispanic American, Asian American, Pacific Islander, or American Indian	31
Relationship between CKD and kidney cancer	
Agree that kidney cancer and CKD can be related	56
Agree that it is possible to get CKD in remaining kidney after nephrectomy for kidney cancer	71
Agree that kidney health protection after nephrectomy is important	94
Agree that a person with kidney cancer can take steps to reduce the risk for CKD	75

Note: N=417.
Abbreviation: CKD, chronic kidney disease.

nephrectomy, and 38% were told about partial nephrectomy; of those who were told about partial nephrectomy, the surgeon recommended against it. Even among patients with early-stage kidney cancer, only 18% underwent partial nephrectomy.

CKD diagnosis and type of nephrectomy

Results in this group were also bothersome in view of radical nephrectomy being a risk factor for CKD. Among the 81 patients (19%) who were given a diagnosis of CKD, 40% received a diagnosis prior to their kidney cancer diagnosis; 53% after, and 7% did not remember when they were given the diagnosis. CKD was diagnosed in 29 patients before they underwent surgery and 79% of them underwent radical nephrectomy. They underwent a radical nephrectomy even though loss of kidney function had been determined prior to surgery.

Knowledge of kidney cancer and kidney health

The results suggest a significant lack of knowledge on the relationship between kidney cancer and overall kidney health (**Table 3**). Only 56% of patients thought that kidney cancer and CKD were somehow related; only 40% thought that losing part or all of a kidney due to an injury or a disease other than cancer is a risk factor for CKD. The educational gap should be remedied, based on one more findings from the study: 81% of respondents thought there are not enough information resources available for kidney cancer and less than one-third were satisfied with current sources of information on this topic.

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Building Awareness of Choices to Promote a Nephron-Sparing Approach

The following interview was conducted with Paul Russo, MD, Memorial Sloan-Kettering Cancer Center, who commented on implications of the survey preceding this section.

KCJ: Dr. Russo, are you surprised by the results of the survey, particularly in view of substantial evidence in recent years making a solid case for expanded use of nephron-sparing surgery?

Dr Russo: I was not really surprised by the results because we knew from national data bases, such as SEER, National Inpatient Sample, and SEER linked to Medicare claims, that in the United States radical nephrectomy was being over utilized in the treatment of small renal masses (T1: tumors of 7 cm or less). Approximately 70-80% of patients were undergoing radical rather than partial nephrectomy in this setting. These statistics are an obvious reflection of the interactions between surgeons and patients and their caregivers. There may be several reasons that kidney sparing operations are underutilized for smaller tumors. Over the last 25 years, very little open kidney surgery was done due to the evolution of endourological and extracorporeal shock wave treatment of stones. In addition, most direct kidney trauma, other than cases where there were other major visceral injuries or the renal pedicle was destroyed, is now managed non operatively with observation only or angio embolization. Unless surgeons are at very high volume medical centers with many kidney tumor patient referrals, the absolute number of kidney operations per surgeon per year is scant and the complex operative skills required to perform partial nephrectomy were not being taught or acquired by trainees. A final factor was the evolution in the last decade of minimally invasive (laparoscopic, robotic assisted) kidney surgery. Even among experts and leaders in the field, partial nephrectomy was considered a challenging operation in which advanced training and skill sets were required. The attractive benefits of less surgical pain and more rapid return to normal activities contributed to the over utilization of these minimally invasive approaches particularly in the management of small kidney tumors. Since the surgeons are the prime advisors to patients and families, their personal knowledge of the disease and surgical skill sets generally provide the primary information to the patients and families.

KCJ: What should be done at the "grass-roots" level, for example within the hospital and its committees, to change protocols and address the knowledge deficit?

Dr Russo: I am a big believer that academic studies will provide the main impetus for changes in clinical practice. A great example of this is the great work in breast cancer over 30 years which brought the field from radical mastectomy for all women to the contemporary practice of lumpectomy, sentinel lymph node mapping, and adjuvant radiation and chemotherapies with marked improvement in quality of life and survival for the patients. In the case of kidney tumors, fundamental understanding from studies completed in the last decade helps us guide the way forward. We now know that approximately 20% of kidney tumors detected today are benign without metastatic potential and 25% are indolent malignancies with limited metastatic potential. There is a wealth of data that indicates that for T1 patients, partial nephrectomy, when technically feasible, provides the same oncological outcomes as radical nephrectomy. These facts coupled with the emerging realization that chronic kidney disease (CKD) is far more prevalent than we previously understood (affecting over 30 million Americans) and is due to common medical conditions such as hypertension, diabetes, and cigarette smoking induced vascular disease. The concept that a patient could acquire CKD, or have preexisting CKD worsened by unnecessary radical nephrectomy and now at increased risk for cardiovascular events and worse overall survival lessened the appeal of radical nephrectomy for small renal tumors by any technique. Educational seminars and workshops, academic meetings and press releases of important kidney cancer studies, and up to date web sites for hospitals and urology departments can all function to

"There is a wealth of data that indicates that for T1 patients, partial nephrectomy, when technically feasible, provides the same oncological outcomes as radical nephrectomy."

improve both patient and physician awareness regarding the value of kidney preservation. In addition, the more liberal use of active surveillance strategies for elderly and comorbidly ill patients with small renal masses has gained traction with many studies indicating that this is a safe approach in the vast majority of such patients. Surgical guideline committees (AUA, EUA) have now incorporated many of these principles urging surgeons to perform kidney sparing approaches whenever possible and are easily retrievable by both patients and physicians alike.

KCJ: What studies are pivotal to motivating community-based oncologists and surgeons to reconsider their policies and change their behavior? Are references 10-18 in the reference list at the end of the *Am J Kidney Dis*. 2013;61;939-946)article a good start?

Dr Russo: These studies are definitely a good start. The combination of increasing the awareness of the seriousness of chronic kidney disease and its widespread prevalence coupled with the above discussed oncological principles regarding best management of the small renal mass should enable patients and physicians to conclude that kidney sparing strategies should be employed whenever possible.

KCJ: What is being done at MSKCC to put practice more in line with the take-home messages from the survey?

Dr Russo: For over 10 years at MSKCC we have stressed kidney preservation as our principle approach to the small renal mass. Over 90% of T1a tumors (<4 cm) and over 60% of T1b tumors (<7cm) are managed by partial nephrectomy whether operations were performed by open or minimally invasive technique. The proportion of kidney sparing operations reported at (2013; is the exact opposite reported in the studies examining practice patterns across the country using the above mentioned large data sets. We also liberally apply active surveillance approaches to elderly and medical vulnerable patients with small renal masses with very few (<5%) of these carefully selected patients ultimately required surgical intervention.

"We also liberally apply active surveillance approaches to elderly and medical vulnerable patients with small renal masses with very few (<5%) of these carefully selected patients ultimately required surgical intervention."

KCJ: Do you have any results at MSKCC that could be a model and do you intend to follow up with another article on the topics covered in the *Am J Kidney Dis* article?

Dr Russo: At MSKCC, referral services, nursing staff, and physicians alike are well versed on the above described kidney sparing principles. Patients understand the medical benefits of maximizing kidney function over a life time and following their consultations often leave understanding that preventing CKD is a goal on par with resecting a small kidney tumor particularly since nearly half of these tumors have benign or indolent pathology. Our websites stress these principles and tend not over emphasize the technical aspects of treatment. It is clear that our skilled surgeons can accomplish partial nephrectomy with low rates of complications and hospital stays of 2 days by both open or minimally invasive approaches. Within the patient and caregiver oriented data obtained in the survey commissioned by National Kidney Foundation are many other researchable topics of great interest that we plan to pursue, particularly related to the quality of life for patients with more advanced disease. KCJ

formation and Publications, NCCN. "Together, we will identify and fund projects that interweave patient support and information, health care systems issues, and broadening of clinician knowledge base to improve the quality of care for individuals with rare cancers."

The NCCN ORP and Pfizer will announce an RFP seeking concepts for initiatives focusing on the following areas where there are gaps in care:

- Health care provider education and incorporation of education into practice.
- Provider/patient communications and treatment decision-making.
- Increasing the use of evidence-based recommendations for management of renal cell carcinoma or hematologic malignancies.
- Information related to patient assistance programs and other patient-centered resources.

Organizations may submit for one of two categories: renal cell carcinoma or hematologic malignancies, which will include acute lymphoblastic leukemia (ALL), chronic myelogenous leukemia (CML), and non-Hodgkin's lymphomas (NHL).

Report from Euro Cancer Meeting: Similar Phase 3 Results for Dovitinib vs Sorafenib in Metastatic RCC

AMSTERDAM — Dovitinib failed to show superior efficacy in a head to head comparison with sorafenib in patients with metastatic renal cell carcinoma (mRCC) who had progressed following therapies targeting the VEGF and mTOR pathways. However, this large, phase 3 trial did establish a role of tyrosine kinase inhibitors in that setting. Dovitinib showed similar activity to sorafenib and generally a well tolerated safety profile. It may offer an additional treatment alternative in this group of with limited treatment options.

Findings were presented in September during the Genitourinary Malignancies Proffered Papers Session (Abstract E17-7035) at the 17th ECCO – 38th ESMO – 32nd ESTRO European Cancer Congress in Amsterdam, The Netherlands. The congress was part of a series of European Cancer Congresses that are organized in joint partnership with ESSO, EACR, EONS and SIOPE to offer multidisciplinary and multi-professional educational opportunities in oncology.

Citing the unmet need for treatments of patients with mRCC who progress on therapies that target the VEGFR and mTOR pathways, Robert Motzer, MD, of the Memorial Sloan Kettering Cancer Center (MSKCC), New York, presented late breaking results from a direct comparison of dovitinib and sorafenib.

This is an important randomized phase 3 trial that compared two TKIs in the third line setting. Patients included in the study had progressed after at least one prior VEGF targeted therapy and one prior mTOR inhibitor. For such patients novel treatment options are urgently needed. Dovitinib (TKI258), targeting not only the VEGFR, PDGFR and ckit but also the FGFR 1-3, which may play a role in the mechanisms of escape from VEGF-targeted therapies, was in fact promising and reasonable to study in this patient population. Although this study is a negative study, not showing an improvement in progression free survival with dovitinib over sorafenib, important data was generated. Very few objective responses (4%) were seen, but a disease stabilization in about half of the patients. The benchmark of a nearly 4 months PFS and an 11 months OS in third line patients has been established. Novel therapies for metastatic renal cell cancer will have to outreach these results. KCJ

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