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Kidney Cancer JOURNAL

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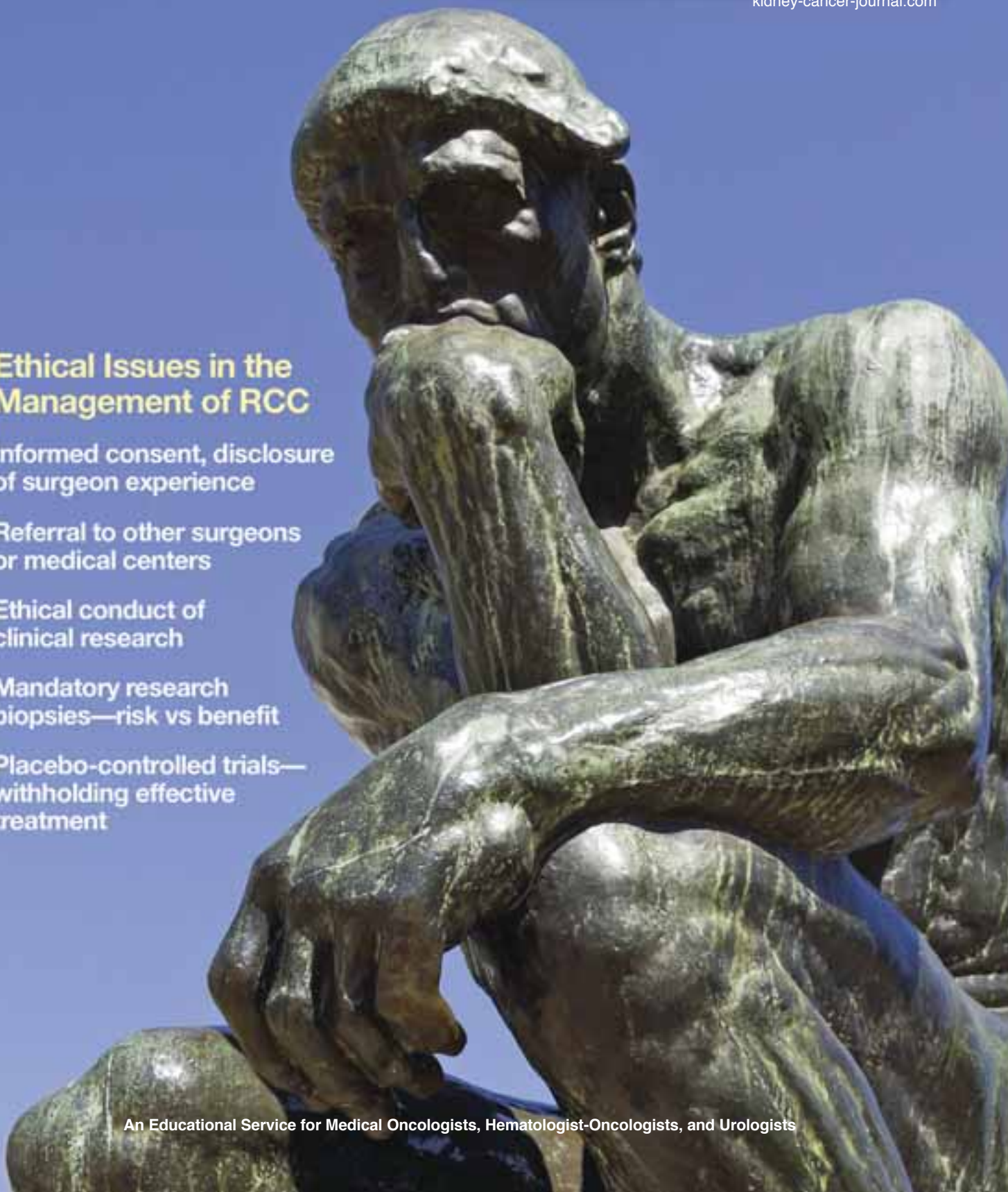

Ethical Issues in the Management of RCC

Informed consent, disclosure of surgeon experience

Referral to other surgeons or medical centers

Ethical conduct of clinical research

Mandatory research biopsies—risk vs benefit

Placebo-controlled trials—withholding effective treatment

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

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

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About the Cover
A special report on ethical issues in renal cell carcinoma highlights controversies likely to arise, many of them related to clinical trials. Photo depicts the Thinker, created in 1902 by Auguste Rodin.

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KCJ EDITOR'S MEMO

Finding the "Devil in the Details" in Managing Kidney Cancer

Robert A. Figlin, MD

One of the more intriguing idioms is the expression, "the devil is in the details," which means that mistakes are usually made in the small details of a project. Usually it is a cautionary tale, involving the need to pay attention to avoid failure, an expression of the concept that many things seem straightforward on the surface, but difficulties, problems, and obstacles are later discovered while trying to implement or execute a task or plan.

Although it seems somewhat of a cliché these days, it still has universal application, including our oncology practices where the details and nuances of our relationships with patients, their families and other health care providers can lead to difficult circumstances. On the other hand, and in a purely clinical context, careful attention to detail and nuance, especially in view of new findings from the literature, can have impact on how we interpret results on a renal mass and determining the extent of risk.

Our main article in this issue suggests how "the devil is in the details" can raise implications for what we do in managing renal cell carcinoma. Yes, all of this may seem intuitive but the implications are significant. As the article on ethical questions illustrates, "the need to disclose physician-specific factors (experience, previous outcomes, training), is controversial. Studies have correlated surgeon volume and objective ratings of surgeon skill with patient outcomes; these findings suggest that disclosure of these surgeon-specific factors may be relevant to patients' informed decision making. A survey of patients supported this, as a majority of respondents found information on surgeon volume and outcomes essential."

The issue of disclosure of surgeon experience is very relevant to the surgical management of renal cancer, as Dr Eric Singer and Dr Parth Modi point out. Laparoscopic and robotic-assisted partial nephrectomy have become popular and widely utilized interventions for small renal masses. Several studies have demonstrated a learning curve with the use of these surgical modalities and surgeon experi-

(continued on page 17)

INLYTA® (axitinib)

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

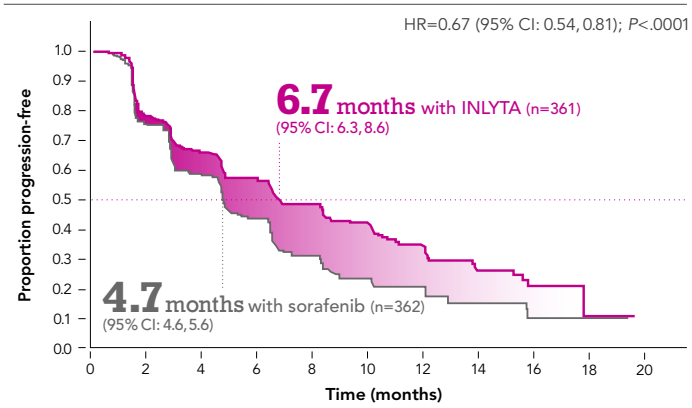
Choose a 2nd-line **treatment** with 2nd-line **evidence**

The ONLY treatment option with superior phase 3 efficacy vs an active comparator, sorafenib, in 2nd-line mRCC*

*Based on MEDLINE® literature review for phase 3 trials in metastatic RCC (mRCC) as of August 2014.

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

Primary endpoint: progression-free survival (PFS)



- **AXIS is the ONLY positive phase 3 trial that was designed to evaluate an exclusively 2nd-line patient population[1†]**

†Based on MEDLINE® literature review for phase 3 trials in mRCC as of August 2014.

- **National Comprehensive Cancer Network® (NCCN®) category 1 recommendation**

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Kidney Cancer include axitinib (INLYTA) as a category 1 recommendation in patients with advanced predominantly clear-cell RCC who have failed one prior systemic therapy[3]

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
- **Cardiac failure** has been observed and can be fatal. Monitor for signs or symptoms of cardiac failure throughout treatment with INLYTA. Management of cardiac failure may require permanent discontinuation of INLYTA
- **Gastrointestinal perforation and fistula**, including death, have occurred. Use with caution in patients at risk for gastrointestinal perforation or fistula. Monitor for symptoms of gastrointestinal perforation or fistula periodically throughout treatment
- **Hypothyroidism** requiring thyroid hormone replacement has been reported. Monitor thyroid function before initiation of, and periodically throughout, treatment
- No formal studies of the effect of INLYTA on **wound healing** have been conducted. Stop INLYTA at least 24 hours prior to scheduled surgery
- **Reversible Posterior Leukoencephalopathy Syndrome (RPLS)** has been observed. If signs or symptoms occur, permanently discontinue treatment
- Monitor for **proteinuria** before initiation of, and periodically throughout, treatment. For moderate to severe proteinuria, reduce the dose or temporarily interrupt treatment
- **Liver enzyme elevation** has been observed during treatment with INLYTA. Monitor ALT, AST, and bilirubin before initiation of, and periodically throughout, treatment
- For patients with moderate **hepatic impairment**, the starting dose should be decreased. INLYTA has not been studied in patients with severe hepatic impairment
- Women of childbearing potential should be advised of potential hazard to the fetus and to avoid becoming **pregnant** while receiving INLYTA
- Avoid strong **CYP3A4/5 inhibitors**. If unavoidable, reduce the dose. Grapefruit or grapefruit juice may also increase INLYTA plasma concentrations and should be avoided
- Avoid strong **CYP3A4/5 inducers** and, if possible, avoid moderate CYP3A4/5 inducers
- The **most common (≥20%) adverse events (AEs)** occurring in patients receiving INLYTA (all grades, vs sorafenib) were diarrhea, hypertension, fatigue, decreased appetite, nausea, dysphonia, hand-foot syndrome, weight decreased, vomiting, asthenia, and constipation
- The **most common (≥10%) grade 3/4 AEs** occurring in patients receiving INLYTA (vs sorafenib) were hypertension, diarrhea, and fatigue
- The **most common (≥20%) lab abnormalities** occurring in patients receiving INLYTA (all grades, vs sorafenib) included increased creatinine, decreased bicarbonate, hypocalcemia, decreased hemoglobin, decreased lymphocytes (absolute), increased ALP, hyperglycemia, increased lipase, increased amylase, increased ALT, and increased AST

Please see brief summary on the following pages.

Inlyta®
axitinib 1mg and 5mg tablets

INLYTA® (AXITINIB) TABLETS FOR ORAL ADMINISTRATION

Initial U.S. Approval: 2012

Brief Summary of Prescribing Information

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

DOSAGE AND ADMINISTRATION

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

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

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

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

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

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

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

DOSAGE FORMS AND STRENGTHS

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

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

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

Cardiac Failure. In a controlled clinical study with INLYTA for the treatment of patients with RCC, cardiac failure was reported in 6/359 patients (2%) receiving INLYTA and 3/355 patients (1%) receiving sorafenib. Grade 3/4 cardiac failure was observed in 2/359 patients (1%) receiving INLYTA and 1/355 patients (<1%) receiving sorafenib. Fatal cardiac failure was reported in 2/359 patients (1%) receiving INLYTA and 1/355 patients (<1%) receiving sorafenib. Monitor for signs or symptoms of cardiac failure throughout treatment with INLYTA. Management of cardiac failure may require permanent discontinuation of INLYTA.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DRUG INTERACTIONS

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

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

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

USE IN SPECIFIC POPULATIONS

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

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

Oral axitinib administered twice daily to female mice prior to mating and through the first week of pregnancy caused an increase in post-implantation loss at all doses tested (≥15 mg/kg/dose, approximately 10 times the systemic exposure (AUC) in patients at the recommended starting dose).

In an embryo-fetal developmental toxicity study, pregnant mice received oral doses of 0.15, 0.5 and 1.5 mg/kg/dose axitinib twice daily during the period of organogenesis. Embryo-fetal toxicities observed in the absence of maternal toxicity included malformation (cleft palate) at 1.5 mg/kg/dose (approximately 0.5 times the AUC in patients at the recommended starting dose) and variation in skeletal ossification at ≥0.5 mg/kg/dose (approximately 0.15 times the AUC in patients at the recommended starting dose).

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

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

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

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

No dosage adjustment is required in elderly patients.

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

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

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

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

OVERDOSAGE

There is no specific treatment for INLYTA overdose.

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

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

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

NONCLINICAL TOXICOLOGY

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

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

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

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

PATIENT COUNSELING INFORMATION

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

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

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

Rx only August 2014

References: 1. Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomized phase 3 trial. *Lancet.* 2011;378(9807):1931-1939. **2.** Data on file. Pfizer Inc, New York, NY. **3.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Kidney Cancer V.3.2014. © National Comprehensive Cancer Network, Inc 2014. All rights reserved. Accessed July 1, 2014. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

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

Kidney Cancer Journal Author Guidelines

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

References

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

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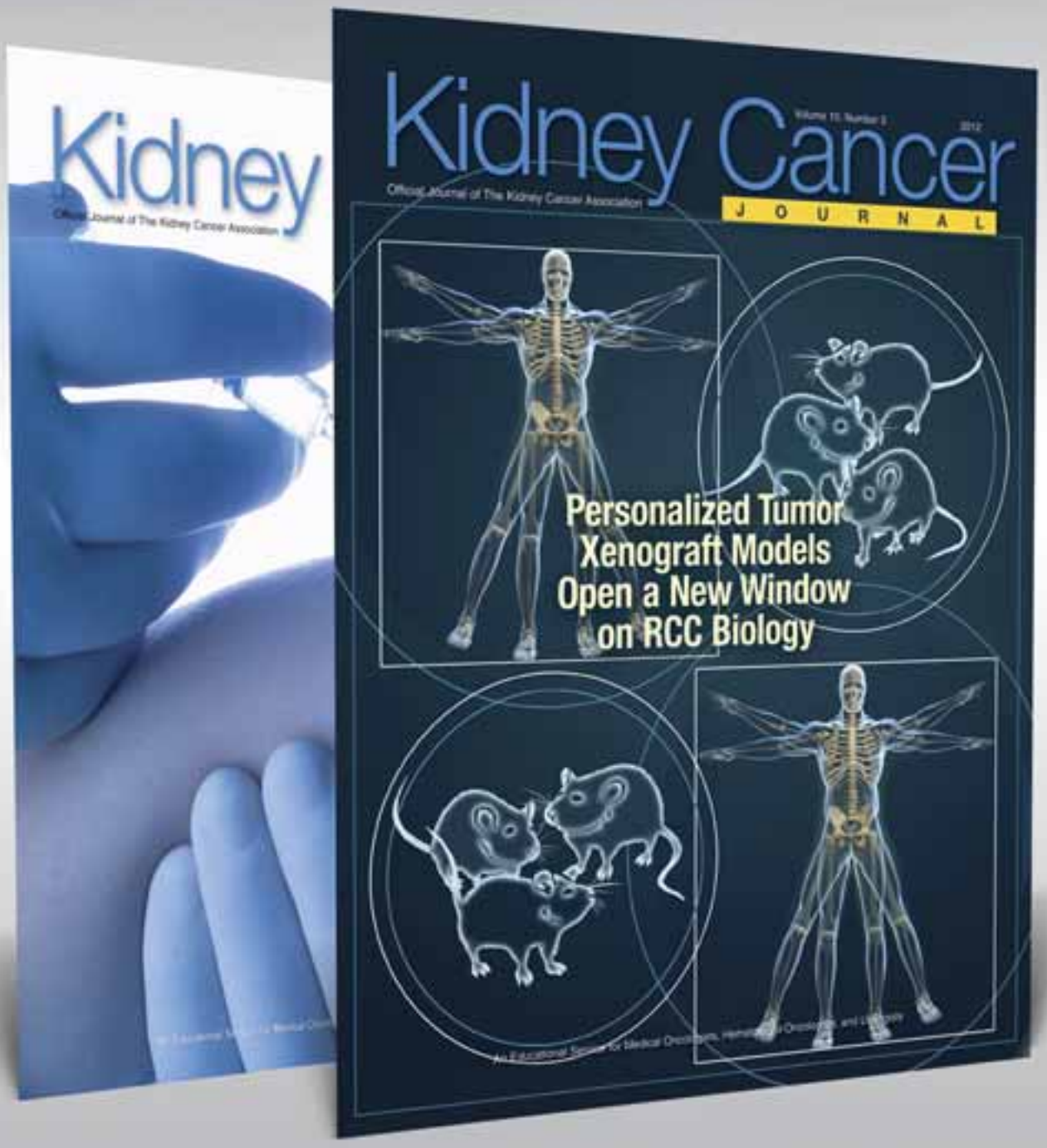

Essential Peer-Reviewed Reading in Kidney Cancer

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

HIF-2 dependent lipid storage promotes endoplasmic reticulum homeostasis in clear cell renal cell carcinoma. Qiu B, Ackerman D, Sanchez DJ, et al. *Cancer Discov*. 2015; Mar 31. pii: CD-14-1507. [Epub ahead of print]
Summary: Two hallmarks of clear cell renal cell carcinoma (ccRCC) are constitutive hypoxia inducible factor (HIF) signaling and abundant intracellular lipid droplets (LDs). However, regulation of lipid storage and its role in ccRCC are incompletely understood. Transcriptional profiling of primary ccRCC samples revealed that expression of the LD coat protein gene PLIN2 was elevated in tumors and correlated with HIF-2α, but not HIF-1α, activation. HIF-2α dependent PLIN2 expression promoted lipid storage, proliferation, and viability in xenograft tumors. Mechanistically, lipid storage maintained integrity of the endoplasmic reticulum (ER), which is functionally and physically associated with LDs. Specifically, PLIN2 dependent lipid storage suppressed cytotoxic ER stress responses that otherwise result from elevated protein synthetic activity characteristic of ccRCC cells.
Conclusion: In addition to promoting ccRCC proliferation and anabolic metabolism, HIF-2α modulates lipid storage to sustain ER homeostasis, particularly under conditions of nutrient and oxygen limitation, thereby promoting tumor cell survival.

Carbonic anhydrase-IX score is a novel biomarker that predicts recurrence and survival for high-risk, non-metastatic renal cell carcinoma: Data from the phase III ARISER clinical trial. Chamie K, Klöpfer P, Bevan P, et al. *Urol Oncol*. 2015 Mar 27. pii: S1078-1439(15)00076-9. doi: 10.1016/j.urolonc.2015.02.013. [Epub ahead of print]
Summary: Studies have recently called into question the role of CAIX as a biomarker for ccRCC. To investigate this uncertainty, this study quantified the association of CAIX with lymphatic involvement and survival using data from ARISER study (WX-2007-03-HR)-a prospective trial involving subjects with high-risk nonmetastatic ccRCC. Results are based on the records of 813 patients enrolled in the ARISER study. Central review of histology, grade, and CAIX staining (frequency and intensity) was performed. CAIX score was derived by multiplying the staining intensity (1-3) by percent positive cells (0%-100%), yielding a range of 0 to 300.Tthe association of CAIX expression and score with lymphatic spread and survival (disease-free survival [DFS] and overall survival [OS]) was determined. Median follow-up of the cohort was 54.2 months. Although 56% of subjects with lymphatic involvement had CAIX>85%, only 33% had CAIX score≥200. On multivariable analysis, CAIX>85% was not a statistically significant predictor of DFS and OS ($P = 0.06$ and $P = 0.15$, respectively). However, CAIX score≥200, when compared with CAIX score≤100, was associated with improved DFS and OS ($P = 0.01$ and $P = 0.01$, respectively) on multivariable analysis.
Conclusion: The largest, multicenter, prospective analysis of patients with high-risk nonmetastatic ccRCC demonstrates the utility of CAIX score as a statistically significant prognostic biomarker for survival. CAIX score should be quantified for all patients with high-risk disease after nephrectomy.

Predicting renal parenchymal loss following nephron sparing surgery. Meyer A, Woldu SL, Weinberg AC, et al. *J Urol*. 2015 Mar 25. pii: S0022-5347(15)03460-6. doi: 10.1016/j.juro.2015.03.098. [Epub ahead of print]
Summary: This report analyzed the relationship between various patient, operative, and tumor characteristics to determine which factors correlate with renal parenchymal volume (RPV) loss after nephron sparing surgery (NSS) using a novel 3-dimensional (3-D) volume assessment. This was a retrospective review of institutional database from 1992-2014 of patients undergoing NSS for a localized renal mass. Tumors were classified according to the R.E.N.A.L. nephrometry system. Using 3-D software, preoperative and postoperative RPV was calculated for the ipsilateral and contralateral kidney; 158 patients were analyzed with mean age 58.7 years and mean follow-up of 40.1 months. The mean preoperative tumor volume was 34.0cc and mean tumor dimension was 3.4cm. The mean R.E.N.A.L. nephrometry score was 6.2, with 60.1%, 34.2%, and 5.7% of tumors classified as low, medium, and high complexity, respectively. The mean change in RPV after NSS was -15.3% for the ipsilateral kidney and -6.8% for the total kidney volume. Ischemia time, tumor size, R.E.N.A.L. nephrometry score, complexity grouping, and the individual nephrometry components of tumor size, percent exophytic, anterior/posterior, depth, and tumor proximity to the renal artery or vein were all associated with larger RPV loss. Only ischemia time, tumor size, posterior location, and percent exophytic were independently associated with more RPV loss.
Conclusion: Precise 3-D volumetric analysis showed that ischemia time, tumor size, and endophytic/exophytic properties of a localized renal mass are the most important determinants of RPV loss.

A Phase II Study of Pazopanib in Patients with Localized Renal Cell Carcinoma to Optimize Preservation of Renal Parenchyma. Rini BI, Plimack ER, Takagi T, et al. *J Urol*. 2015 Mar 23. pii: S0022-5347(15)03398-4. doi: 10.1016/j.juro.2015.03.096. [Epub ahead of print]
Summary: Localized clear cell RCC patients meeting one or both of the following criteria were enrolled in a prospective phase II trial: radical nephrectomy or PN likely to yield GFR<30mL/min/1.73m^2; or PN high risk due to high complexity (RENAL=10-12) or tumor adjacent to hilar

(continued on page 18)

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

Cabozantinib granted fast track designation by FDA for advanced RCC

SOUTH SAN FRANCISCO, CA—The FDA has granted Fast Track designation to cabozantinib for treatment of patients with advanced renal cell carcinoma (RCC) who have received one prior therapy. Cabozantinib is the lead compound of Elixisis and inhibits activity of multiple tyrosine kinases including MET, VEGFRs and RET.

Fast Track designation confers important benefits, including potential eligibility for Priority Review of a New Drug Application, if relevant criteria are met. Cabozantinib is the subject of METEOR, an ongoing phase 3 pivotal trial in patients with metastatic RCC who have experienced disease progression following treatment with at least one VEGFR tyrosine kinase inhibitor.

Patients are randomized 1:1 to receive 60 mg of cabozantinib daily or 10 mg of everolimus daily. The primary endpoint of METEOR is progression-free survival, and secondary endpoints include overall survival and objective response rate. Exelixis expects to release top-line results from the trial in the second quarter of 2015. In addition to the metastatic RCC development program, Exelixis is also evaluating cabozantinib in CELESTIAL, a phase 3 pivotal trial in second-line hepatocellular carcinoma (HCC).

Key statistics about kidney cancer for 2015

The American Cancer Society's most recent estimates for kidney cancer in the United States are for 2015:

- About 61,560 new cases of kidney cancer (38,270 in men and 23,290 in women) will occur.
- About 14,080 people (9,070 men and 5,010 women) will die from this disease. The average age when the disease is diagnosed is 64.

Highlights from 2015 ASCO GU Symposium: adjuvant TKIs, prognostic markers, and impact of BMI on survival

ORLANDO, FL—The 2015 ASCO Genitourinary Symposium covered a broad spectrum of topics, including initial results from the ASSURE trial on adjuvant TKI use, and intriguing results on prognostic markers not ready for application but deserving of future study that could have an impact on data presented at the larger ASCO meeting in June.

In the ASSURE trial, A total of 1943 patients with resected T1b–T4, any grade N, renal cell carcinoma were randomly assigned to adjuvant sunitinib, sorafenib, or placebo, and treated up to 1 year. At an interim analysis, with 62% of data, the study did not meet its primary endpoint of disease-free survival. Survival was equivalent in both treatment and placebo arms. The authors conclude that adjuvant treatment with sorafenib or sunitinib should not be pursued in this population of patients. (Abstract 403)

What is the significance of neutrophil to lymphocyte ratio (NLR) as a prognostic and predictive marker? In another study, change in NLR was evaluated as a predictive marker of response to targeted therapy. NLR was found to be an independent prognostic factor for survival after controlling for IMDC criteria, and NLR conversion may be an early biomarker for positive response to targeted therapy. (Abstract 404)

An evaluation was conducted of 4657 patients with metastatic renal cell carcinoma (mRCC) who were treated in phase II and III studies between 2003 and 2013 to determine the relationship between BMI on survival and overall response rate. After adjusting for risk factors, patients with BMI ≥25 kg/m^2 had a longer overall survival compared with those with BMI <25 kg/m^2 (23.4 months vs 14.5 months; HR, 0.830; $P = .0008$). Patients with BMI ≥25 kg/m^2 also had a higher progression-free survival (HR, 0.821; $P < .0001$) and overall response rate (OR, 1.527; $P< .001$). (Abstract 405)

At 2015 AACR Meeting: Promising data emerges on first inhibitor of HIF-2α for RCC

PHILADELPHIA—Preclinical data indicates that a new compound, PT2385, suppresses gene expression essential for tumor growth, proliferation, and angiogenesis Peloton Therapeutics, Inc., a drug discovery and development company focused on advancing first-in-class, small molecule cancer therapies targeting unexploited molecular vulnerabilities, presented preclinical data on its lead investigational candidate, PT2385, at the American Association for Cancer Research Annual Meeting in Philadelphia. PPT2385 is the first clinical stage antagonist of hypoxia inducible factor-2α (HIF-2α), a transcription factor implicated in the development and progression of renal cancer.

"HIF-2α can act as a tumorigenic driver in cancer. As a transcription factor, HIF-2α has historically been seen by the scientific com-munity as impossible to directly target," said Eli Wallace, PhD, Vice President of Chemistry for Peloton. "Our preclinical evidence indicates that PT2385 is potent, selective, and readily absorbed. We believe this program has the potential to become a significant therapy for renal cancer."

PT2385 is currently being investigated in a Phase 1 clinical trial for the treatment of advanced or metastatic clear cell renal cell carcinoma (ccRCC). Loss of the von Hippel-Lindau tumor suppressor (*VHL*) is the key oncogenic event in up to 95% of patients with ccRCC. With the loss of the VHL protein (pVHL), the transcription factor HIF-2α accumulates and drives the unbalanced expression of numerous gene products. Preclinical data indicate that orally bioavailable PT2385 disrupts HIF-2α activity in ccRCC and thereby blocks the expression of multiple tumorigenic factors responsible for unrestrained cancer cell growth and proliferation, tumor angiogenesis, and suppression of anti-tumor immune responses characteristic of ccRCC.

"Loss of VHL, and resulting activation of HIF-2α, is the signature driving event in clear cell renal cell carcinoma but HIF-2α had been largely dismissed as 'undruggable,' which is one reason the potential of PT2385 is so exciting," remarked William G. Kaelin, Jr., MD, Professor in the Department of Medicine at the Dana-Farber Cancer Institute, Harvard Medical School, a scientific advisor to Peloton, and a noted expert on *VHL* and hypoxia inducible factors. "PT2385 is the first molecule to advance to the clinic that binds directly and specifically to HIF-2α and potently inhibits its transcriptional activity." KCJ

Ethical Issues in the Management of Renal Cell Carcinoma: Creating a Framework for Resolving Complex Questions

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Introduction

Kidney cancer is a common and lethal cancer; in 2014 it will account for an estimated 61,560 new diagnoses and 14,080 deaths in the United States alone.[1] The clinical care of affected patients, as well as participation in clinical research involving kidney cancer, poses many potential ethical challenges for the clinician and investigator. The issues discussed in this review, while commonly encountered in this setting, are not exclusive to kidney cancer and will be relevant to many facets of medical care and clinical research.

Informed Consent, Disclosure of Surgeon Experience and Outcomes

Surgical therapy is the mainstay of treatment for renal cell carcinoma[2] and, therefore, issues of informed consent prior to surgical intervention are paramount. The concept of informed consent developed in the early 20th century as advances in surgical and anesthetic techniques made elective surgery possible.[3] Today, informed consent is well-accepted as a central aspect of the surgeon-patient relationship. Traditional informed consent has required the surgeon to disclose certain procedure-specific factors: potential surgical complications and risks, benefits of the proposed surgery, available alternatives and likely outcomes of the treatment. The American Urological Association goes even further in its Code of Ethics, requiring the surgeon to provide the patient with "*all of the information necessary to consent and to make his own choice of treatment, regardless of my own advice or judgment. The information provided must include known risks and benefits, costs, reasonable expectations and possible complications, available alternative treatments and their cost, as well as the identification of other medical personnel who will be participating directly in the care delivery*".[4]

The need to disclose physician-specific factors (experience, previous outcomes, training), however, is more controversial. Studies have correlated surgeon volume[5] and objective ratings of surgeon skill[6] with patient outcomes; these findings suggest that disclosure of these surgeon-specific factors may be relevant to patients' informed decision making. A survey of patients supported this, as a majority of respondents found information on surgeon volume and outcomes essential.[7] Legal opinion on this matter, however, is conflicted. Many states have adopted a "reasonable person" standard for determining the content of an informed consent discussion[3,8] and two State Supreme Courts have addressed the specific issue of surgeon experience.[9] In 1996, the Wisconsin State Supreme Court held that physician experience and outcomes as compared to other physicians' is a meaningful part of the "alternative treatment options" that need to be discussed during the process of informed consent.[9] In 2001, however, the Pennsylvania State Supreme Court defined informed consent as including procedure-specific factors only and categorized information about the physician as outside of the scope of informed consent.[9]

The ethical principle of autonomy is central to this debate. If knowledge of surgeon experience is necessary for patient decision making, its disclosure enhances patient autonomy and therefore is appropriate. While the Wisconsin Supreme Court categorized this information as an important aspect of "surgical alternatives", Clarke and Oakley[10] argue that surgeon ability is an important risk factor, and therefore an essential component of any informed consent discussion. While accepting the importance of patient autonomy, Burger reasons that disclosure of surgeon-specific performance information is only imperative if it is accurate enough to affect patient decision-making.[9] She contends that physician-specific outcomes

Keywords: ethical issues, renal cell carcinoma, informed consent, clinical trials, placebo-controlled trials, surgeon referrals.

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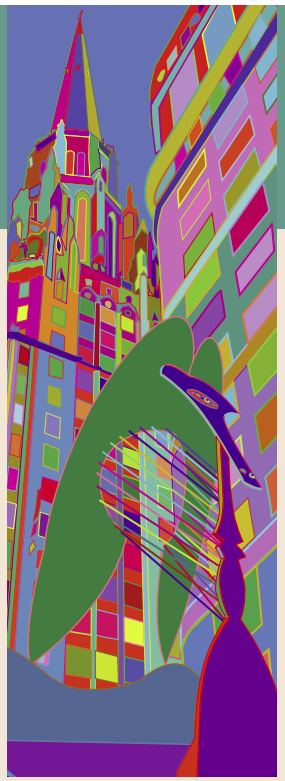

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data is often tied to arbitrary end-points, can be manipulated by patient selection, and is unfairly biased against younger surgeons.[9]

The issue of disclosure of surgeon experience is very relevant to the surgical management of renal cancer. Laparoscopic and robotic-assisted partial nephrectomy have become popular and widely utilized interventions for small renal masses.[11] Several studies have demonstrated a learning curve with the use of these surgical modalities and surgeon experience has been shown to independently predict patient outcomes.[12] Whether currently available individual surgeon-level data is of high enough quality to impact patient decision-making is unclear. Nevertheless, most authors agree that providing this information when asked by the patient is imperative to maintain an open and honest physician-patient relationship.[8] With patients' increasing use of internet data sources, the proliferation of physician rating systems, and a widespread interest in healthcare quality improvement, the question of individual physician-level outcomes data is likely to be an area of discussion for the foreseeable future.

Referral to Other Surgeons or Medical Centers

The optimal management of kidney cancer adds another facet to this discussion - that of referral to other surgeons. Surgeons are sometimes reluctant to refer a patient to another surgeon for multiple reasons: to keep patients close to home and their local health system, to avoid the loss of income from performing surgery, and to avoid the loss of referrals from primary care providers.[13] In this era of rapidly advancing technology, there are multiple surgical options for renal cancer utilizing new instruments and surgical techniques.[14] It is reasonable to expect that not all urologic surgeons will be able to provide every available option to a patient seeking minimally-invasive surgery, nephron-sparing approaches, cytoreductive nephrectomy, or care in other complex situations (i.e. solitary kidney, local recurrence after therapy, familial renal cancer syndrome, etc.). The referral of a patient who would be best served by a procedure that one cannot offer, or not offer well, is relatively easy to accept. More difficult, however, is the question: is a surgeon ethically obliged to refer a patient to another surgeon or institution who reports better results?

The American Urological Association advises each surgeon to "*respect my colleagues, seek their counsel when in doubt about my own abilities, and assist my colleagues whenever requested. I will accept that "competence" includes having adequate and proper knowledge to make professionally appropriate and acceptable decisions regarding management of the patient's problems, as well as the ability and skill to perform what is necessary to be done and to ensure that the aftercare is the best available to the patient*".[4] While this guidance emphasizes the need for honest evaluation of a surgeon's own competence and the humility to seek assistance when needed, it does not address the question of referral to another provider or medical center based on outcomes data or for procedures that he or she does not offer.

An analogous question has been discussed in the thoracic surgery literature.[13] In support of the obligation to refer, Kouchoukos argues that not referring the patient to a more experienced surgeon is unethical as it places self-interest above the patient's best interest. He concedes that there are no clearly established guidelines for this situation, but the ethical principle of avoiding harm (non-maleficence) and general professionalism should compel a referral to a more-experienced and better performing surgeon.[13] Cohn, on the other hand, argues that such a referral is not an ethical imperative. While having the best surgeon in the world operate on every patient may seem ideal, he argues, it is not possible nor is it truly desirable.[13] Cohn contends that it would not be physically possible for a small group of experienced surgeons to perform all of one type of surgery and it would undesirable to limit the dissemination of knowledge of a new technique.[13] Ultimately, both authors agree that there are certain situations (i.e. a procedure with which a surgeon has no experience or one which requires a vast expenditure of resources or coordinated team) in which referral to a more experienced surgeon is ethically necessary. As universally applicable guidance on this issue is not likely to be produced, each surgeon must, in the context of honest discussion with patients, make such decisions on a case-by-case basis.

While individual physician-level data collection has not been widely adopted, the UK National Health Service (NHS) has published nephrectomy data that includes mortality, complications, and length of stay. This data, collected by the British Association of Urological Surgeons (BAUS), has recently been the source of significant controversy due to errors.[15,16] These errors have led to a recommendation from the BAUS to revise or close the NHS website hosting this data.[17] This experience underscores concerns that the problems inherent in widespread public reporting of individual surgeon-level data can compromise the quality of any analysis drawing on such data. Furthermore, the effects of these data on patient selection strategies and access to surgical treatment for high-risk patients are not yet fully understood.

When considering the question of referral to a higher-volume or better performing institution, many of the same issues exist: questions of patient-selection, fear of lost revenue and the quality of publicly-reported data can diminish enthusiasm for referral to high volume centers. Nevertheless, Becker et al. examined the hospital volume-outcome relationship for nephrectomy and found that patients treated at lower-volume hospitals were at higher risk of adverse outcomes.[18] Smaldone et al demonstrated that the use of partial nephrectomy for small renal masses increased as hospital volume increased.[19] Monn and colleagues demonstrated that high hospital volume is associated with fewer blood transfusions and complications after robotic assisted partial nephrectomy.[20] The movement towards regionalization for cancer care has occurred in multiple fields of oncology, including prostate and

bladder cancer.[21]

One resource for the transfer of cancer patients in the United States is the National Cancer Institute's (NCI) cancer center program. Forty-one institutions have been designated "Comprehensive Cancer Centers" by the NCI and are centers of excellence in the research and clinical care of oncology patients. Patients treated at NCI-designated cancer centers have been shown to have lower surgical mortality rates,[22] improved post-operative and long-term survival,[23] and a higher number of harvested lymph nodes[24] for various malignancies. While the outcomes of kidney cancer patients treated at NCI-designated centers have not been specifically studied, these data make a compelling case for regionalization.

Clinical Research

Clinical research aims to advance our understanding of the pathophysiology and treatment of disease and ultimately to improve the care and health of the patient.[25] Unfortunately, such research often carries a risk of harm to participating subjects. Possible harms include side effects and complications of treatment, loss of confidentiality, and exposure to additional procedures or tests. Balancing these risks with benefits is essential for the ethical conduct of clinical research. Several policy statements exist to guide researchers; these include the Nuremberg Code,[26] the Declaration of Helsinki,[27] and the Belmont Report.[28] All of these documents emphasize the importance of protecting the research subject and ensuring respect for subjects' rights. While these documents have laid the historical and ethical framework for modern research ethics, they are not without limitations. Some have argued that the Nuremberg Code, drafted in response to the atrocities perpetrated by Nazi doctors in World War II, is inadequate in its protection of research subjects and provides loopholes for the conduct of unethical research.[29] The Declaration of Helsinki, a document that has undergone several revisions since its initial adoption in 1964, has been criticized as being too restrictive and vague in its recommendations regarding placebo-controlled and phase 1 clinical trials.[30] The Belmont Report, which emphasizes the ethical principles of autonomy, beneficence and justice, does not provide guidance on how to navigate situations in which these principles come into conflict with each other.[28]

In 2000, Emanuel and colleagues proposed a universal list of requirements for ethical research[25] (**Table 1**). The seven elements described below are, the authors propose, like a constitution – a good framework for the ethical conduct of research, but in need of occasional interpretation and revision.[25] As a framework, it is a flexible set of rules that is broadly applicable to human research across many domains: all phases of clinical trials, oncology and non-oncology studies, and research done in both developed and economically developing communities.

Mandatory Research Biopsies

Having presented some guidelines for the ethical conduct of clinical research in general, we turn now to a discussion of some specific issues in kidney cancer research. One issue is that of mandatory research biopsies. Traditionally, renal mass biopsies were used sparingly and in limited clinical scenarios. The expansion of efficacious targeted agents in metastatic renal cell cancer has increased the desire for pre- and post-treatment renal mass research biopsies.[31] Additionally, improvements in image-guided biopsy technique and increased incidental diagnosis of small renal masses have led to renewed interest in the utility of biopsy for small, localized renal masses.[31] One study has demonstrated that patients can be assigned to surgery or surveillance with 97% agreement between biopsy and final pathology.[32] Unlike renal biopsies performed in the course of the clinical care of a patient, however, research biopsies will often not provide any direct benefit to the patient. This has led commentators to question the ethics of making such biopsies mandatory in clinical trials.[33-35]

Peppercorn et al[33] argue that research biopsies that are a condition of enrollment in a clinical trial may be coercive to prospective subjects. This argument alludes to the concept of therapeutic misconception – that patients who are considering clinical trials often believe the trial will benefit them in some way that standard therapy will not. Operating under that assumption, patients may feel coerced to agree to a biopsy in order to obtain the benefits of trial participation they implicitly expect. How can we remedy this issue? The solution is not to make research biopsies optional, argue Peppercorn et al, but to ensure that potential subjects understand the nature of the study, how it differs from standard care, and the risks and lack of direct benefit of the biopsy.[33] Furthermore, research biopsies should not be part of a research protocol without "strong scientific rationale, meaningful informed consent and a low to minimal risk of expected complications."[36]

Overman et al evaluated all clinical trials with research biopsies at MD Anderson Cancer Center from 2005-2010 to determine how the scientific rationale for biopsy was presented to subjects, if the biopsy was mandatory, and if the risks and benefits were clearly communicated in the informed consent document.[34] Of 57 clinical trials examined, 67% included at least one mandatory biopsy. Of these, 71% of studies had biopsy as an eligibility criterion. The complication rate of research biopsies was 5.2% (overall) and 0.8% (major). The study found that discussion of biopsy-related risks was inadequate in the informed consent documentation: the discussion of biopsy risks spanned fewer words on average than that of venipuncture, and risks were rarely presented in a site-specific manner.[34] Furthermore, the statistical rationale for number of research biopsies needed was rarely present or adequate.[34]

To better understand the varying roles biopsies can play, Peppercorn et al categorize them into three categories: clinical biopsy, research biopsy for correlative sci-

Table 1. Seven Requirements for Determining Whether a Reserch Trial Is Ethical

Requirement	Explanation	Justifying Ethical Values	Expertise for Evaluation
Social or scientific value	Evaluation of a treatment, intervention, or theory that will improve health and well-being or increase knowledge	Scarce resources and nonexploitation	Scientific knowledge; citizen's understanding of social priorities
Scientific validity	Use of accepted scientific principles and methods, including statistical techniques, to produce reliable and valid data	Scarce resources and nonexploitation	Scientific and statistical knowledge; knowledge of condition and population to assess feasibility
Fair subject selection	Selection of subjects so that stigmatized and vunerable individuals are not targeted for risky research and the rich and socailly powerful not favored for potentially beneficial research	Justice	Scientific knowledge; ethical and legal knowledge
Favorable risk-benefit ratio	Minimization of risks; enhancement of potential benefits; riskes to the subject are proportionate to the benefits to the subject and society	Nonmaleficence, beneficence, and nonexploitation	Scientific knowledge; citizen's understanding of social values
Independent review	Review of the design of the reserch trial, its proposed subject population, and risk-benefit ratio by individuals unaffiliated with the research	Respect for subject autonomy	Scientific knowledge; ethical and legal knowledge
Informed consent	Provision of information to subjects about purpose of the research, its procedures, potential risks, benefits, and alternatives, so that the individual understands this information and can make a coluntary decision whether to enroll and continue to participate	Respect for subject autonomy	Scientific knowledge; ethical and legal knowledge
Respect for potential and enrolled subjects	Repect for subjects by 1. permitting withdrawal from the research 2. protecting privacy through confidentiality; 3. informing subjects of newly discovered risks or benefits; 4. informing subjects of results of clinical research; 5. maintaining welfare of subjects	Respect for subject autonomy and welfare	Scientific knowledge; ethical and legal knowledge; knowledge of particular subject population

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ence, and research biopsy for integral biomarker research.[33] Clinical biopsies are used in the care of the patient and have a direct benefit to the patient. These biopsies may be useful for research if excess tissue is used or stored for future study. Research biopsies for correlative science are used to correlate a novel or known biomarker with a patient's clinical outcome or response to treatment, and will not impact the care of the subject in any way. Finally, research biopsies for integral biomarker studies are used to establish the presence of a biomarker that is necessary for patient enrollment in a study that is assessing or validating that biomarker. Clinical biopsies should be considered ethical based on their risk and benefit to the patient, as the primary utility of this biopsy is in the direct clinical care of the patient. Research biopsies for integral biomarker research, while not providing a definite benefit to the patient, will direct the patient's care by allowing their inclusion in a trial or in a particular arm of a trial. The most ethically challenging research biopsy is that for correlative research. Opponents argue that tissue for this purpose can be often obtained from clinically indicated biopsies or tissue banks, and therefore could be made optional rather than mandatory for many research protocols.[33]

While there is certainly utility to research biopsies, they should not be mandatory without appropriate scientific justification and detailed statistical planning. As with all aspects research, thorough informed consent is essential. The purpose of the biopsy and the risks specific to it, stratified by the site of biopsy, must be discussed with prospective subjects.

Placebo-controlled Trials

Randomized, controlled clinical trials are one of the most important tools of clinical research. The issue of what to use as the control, however, can be controversial. Placebo-controlled studies often raise the greatest concern, and have been used frequently in the targeted therapy era. (**Table 2**)

Emanuel and Miller have compared the merits of

Table 2. Key Phase 3 Trials of FDA-Approved Targeted Therapies for Advanced Renal Cell Carcinoma

Therapy	Target	Treatment Line	Comparison Arm	Primary Endpoint
Axitinib[37]	VEGFR	Second-Line	Sorafenib	PFS
Bevacizumab + IFN-α (AVOREN)[38]	VEGF	First-line	**Placebo** + IFN-α	OS
Bevacizumab + IFN-α (CALGB)[39]	VEGF	First-line	IFN-α	OS
Everolimus[40]	mTOR	VEGFR Failure	**Placebo**	PFS
Pazopanib[41]	VEGFR	First-line or Cytokine Failure	**Placebo**	PFS
Sorafenib[42]	VEGFR	Cytokine Failure	**Placebo**	OS
Sunitinib[43]	VEGFR	First-line	IFN-α	PFS
Temsirolimus[44]	mTOR	First-line	IFN-α	OS

IFN, interferon; mTOR, mammalian target of rapamycin; OS, overall survival; PFS, progression-free survival; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor. Modified from Singer et al[45] with permission.

placebo-control and active-control trials.[46] Placebo-control advocates argue that methodological purity requires the use of placebo as a control group. Often, they argue, new treatments may not demonstrate benefits over an existing therapy due to variances in response, small effect sizes, or spontaneous improvement in some patients.[46,47] Furthermore, proponents claim, even if a treatment isn't better than an existing therapy, it may have fewer side effects or less cost.[46] This argument centers on the idea that placebo controlled trials are the most scientifically sound and therefore should be allowed. Conversely, supporters of an active-control argue that withholding the standard therapy from the control group is not morally acceptable. Additionally, they argue that the superiority of a new intervention over placebo is not as clinically relevant as its ability to show improvement over an active control.[46] Allowing the use of placebo, they argue, would be to prioritize scientific rigor over the well-being of patients.

Emanuel and Miller argue that there are ethical problems with each of these views and that a middle ground is called for.[46] They argue that withholding efficacious medication from a placebo group, even if it does not result in lasting harm, can lead to increased suffering and is therefore unethical.[46] The active-control argument also has flaws, they argue, as it creates a false dichotomy between rigorous science and ethical research.[46] (**Table 1**)

Emanuel and Miller remind us that in order for research to be ethical, it must be methodologically sound, as exposing subjects to any risk without the possibility of scientifically useful results (as in a methodologically unsound study design) is unethical.[25] Further, they contend, the harm of placebo can occasionally be non-existent or so small as to be negligible. Indeed, in many studies the placebo effect can lead to significant clinical improvement. Finally, Emanuel and Miller argue that the use of placebo allows for increased statistical power, and in some cases may allow for meaningful results from a study with fewer participants – therefore exposing overall fewer patients to potential harm from an investigational therapy.[46] In general, they argue, that most scientists will agree that when live-saving or life-prolonging interventions are available and assignment to placebo would significantly increase the chance for harm, it is unethical to randomize patients to placebo[46]. Similarly, in research involving non-serious ailments, where the chance for harm or discomfort is negligible, placebo-control is ethical.[46]

In controversial cases, between these two extremes, placebo controlled trials should only be used when methodologically necessary: there is a high placebo response rate; the condition has a waxing-waning course or spontaneous improvements; existing therapies have serious side-effects or only partial efficacy; the disease is so rare that a trial with active-control would require so many participants as to make the trial not feasible[46]. If these criteria are met, they argue, the use of placebo control should be evaluated for potential risks of death, disability, harm or discomfort.[46,48] Only in the absence of a substantial difference in these risks can a placebo control ethically be used.[46]

While previous revisions of the Declaration of Helsinki prohibited the use of placebo when any active treatment existed for a condition,[48] the most recent revision (2013) allows for the use of placebo controls when "*for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.*"[27]

Daugherty et al emphasize that placebo-control trials can be ethical in oncology as placebo should always be accompanied by the best available palliative and supportive care.[48,49] In many scenarios in advanced cancer, available third- and subsequent-line therapies do not offer a high probability of benefit and do carry the risk of significant toxicities.[50] In this setting, there may be equi-poise, or uncertainty, when comparing placebo with best supportive care to these active control options.[48] Daugherty et al also propose several methodological strategies to minimize the potential harms of placebo. First, the use of clinically relevant surrogate end-points instead of survival can shorten the duration of a study and therefore decrease exposure and risk of harm to subjects.[48] Additionally, creative study methodology such as cross-over and randomized withdrawal designs can minimize ethical dilemmas and potential harms related to the use of placebo controls.[48]

A recent example of the use of placebo in clinical kidney cancer trials is the 2010 Phase III trial of pazopanib in metastatic and locally advanced kidney cancer.[41] This

study compared pazopanib with placebo in patients enrolled from 2006-2007. Around this time, evidence was emerging for the benefits of targeted therapy with tyrosine-kinase inhibitors (TKIs). Furthermore, prior to the widespread adoption of TKI therapy, cytokine-based therapy was the standard of care for advanced renal cancer. The investigators justified the use of placebo in this study by allowing for the enrollment of patients without prior systemic therapy only if "they were living in countries where there were barriers to the access of established therapies."[41] Furthermore, the authors cited limited access to targeted therapies and emerging doubts about the value of cytokine based therapy as their rationale for the use of placebo in this study. The pazopanib trial also raises the issue of performing clinical research in resource-limited settings.

Joffe and Miller, in considering the use of placebo in clinical trials in developing countries, argue that the ideal research design would utilize two comparison groups – the best available (therapeutic, diagnostic, or prophylactic) intervention as well as the local standard of care.[51] This design is the most scientifically sound and allows for the most useful analysis. The most controversial design, as in the case of the pazopanib study, is the use of a local standard of care control only. Critics argue that the use of placebo in this case is a disadvantage to participants as it is inferior to the best available therapy. Joffe and Miller argue, however, that this is a flawed argument that ignores the reality of the alternatives available to potential participants in low-resource settings.[51] If placebo and supportive care is equivalent to the best care available to potential participants, no harm is being done by enrollment in the study. On the contrary, entry into the trial is beneficial as it gives the patient a chance of being assigned to a potentially beneficial therapy. In cases such as this, Joffe and Miller support the use of the "independent clinician" heuristic – "ask how a knowledgeable independent clinician responsible for an eligible patient would advise her, bearing in mind the available treatment options."[51]

The high burden of cancer in the developing world highlights the need for clinical research in low-resource settings.[51] Such research is essential but can be ethically challenging and requires thoughtful experimental design, adherence to established principles of ethical research, as well as consideration of the needs and societal values of host communities.

Conclusion

The field of kidney cancer is robust with clinical scenarios and research questions that may pose ethical dilemmas. In this review, we have attempted to discuss a few of these dilemmas and provide some framework for arriving at a practical and ethically sound solution. We strongly recommend the use of clinical and research ethics consultations when considering complex ethical questions. These resources are invaluable in assisting ethical decision-making as well as involving key stakeholders during routine patient care or the design and conduct of clinical research.

Due to the growth of clinical research in this field as well as the increasing incidence of kidney cancer, continued and nuanced examination of these ethical issues, and others, will be needed. Moreover, an understanding of these issues is an important aspect of the training of clinicians and researchers at all levels.

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References

1. Siegel R, Miller KD, Jemal A. Cancer statistics, 2015. *CA: a cancer journal for clinicians*. 2015;65(1):5-29.
2.Campbell SC, Lane, Brian R. Malignant Renal Tumors. In: Wein AJ, Kavoussi, Louis R., Novick, Andrew C., Partin, Alan W., and Craig A. Peters, ed. *Campbell-Walsh Urology, 10th Ed*. Vol 2. 10th ed. Philadelphia, PA: Elsevier Saunders; 2011:1413-1474.
3. Cainzos MA, Gonzalez-Vinagre S. Informed consent in surgery. *World journal of surgery*. 2014;38(7):1587-1593.
4. Association AU. AUA Code of Ethics. https://www.auanet.org/common/pdf/myaua/Code-of-Ethics.pdf. Accessed 12/10/2014, 2014.
5. Birkmeyer JD, Stukel TA, Siewers AE, Goodney PP, Wennberg DE, Lucas FL. Surgeon volume and operative mortality in the United States. *The New England journal of medicine*. 2003;349(22):2117-2127.
6. Birkmeyer JD, Finks JF, O'Reilly A, et al. Surgical skill and complication rates after bariatric surgery. *The New England journal of medicine*. 2013;369(15):1434-1442.
7. Char SJ LB, Kirkwood KS. How important is disclosing surgeon experience when obtaining informed consent? *J Am Coll Surg* 2011;213(3S): S112–S113.
8. Ganai S. Disclosure of surgeon experience. *World journal of surgery*. 2014;38(7):1622-1625.
9. Burger I, Schill K, Goodman S. Disclosure of individual surgeon's performance rates during informed consent: ethical and epistemological considerations. *Annals of surgery*. 2007;245(4):507-513.
10. Clarke S, Oakley J. Informed consent and surgeons' performance. *The Journal of medicine and philosophy*. 2004;29(1):11-35.
11. Ghani KR, Sukumar S, Sammon JD, Rogers CG, Trinh QD, Menon M. Practice patterns and outcomes of open and minimally invasive partial nephrectomy since the introduction of robotic partial nephrectomy: results from the nationwide inpatient sample. *The Journal of urology*. 2014; 191(4):907-912.
12. Mathieu R, Verhoest G, Droupy S, et al. Predictive factors of complications after robot-assisted laparoscopic partial nephrectomy: a retrospective multicentre study. *BJU international*. 2013;112(4):E283-289.
13. Kouchoukos NT, Cohn LH, Sade RM. Are surgeons ethically obligated to refer patients to other surgeons who achieve better results? *The Annals of thoracic surgery*. 2004;77(3):757-760.
14. Campbell SC, Novick AC, Belldegrun A, et al. Guideline for management of the clinical T1 renal mass. *The Journal of urology*. 2009;182(4):1271-1279.
15. Henderson JM, Fowler S, Joyce A, Dickinson A, Keeley FX, Baus. Perioperative outcomes of 6042 nephrectomies in 2012: surgeon-reported results in the UK from the British Association of Urological Surgeons (BAUS) nephrectomy database. *BJU international*. 2014.
16. Keeley FX. Public reporting of individual surgeons' outcomes in the UK. *The Canadian journal of urology*. 2014;21(5):7429.
17. Surgeons TBAoU. Surgical Outcomes Data. 2014; Nov 2014. Accessed 11/25/2014, 2014.
18. Becker A, Bianchi M, Hansen J, et al. Benefit in regionalization of care for patients treated with nephrectomy: a Nationwide Inpatient Sample. *World journal of urology*. 2014;32(6):1511-1521.
19. Marc Smaldone JS, Daniel Canter, Russell Starkey, Fang Zhu, Karyn Stitzenberg, Alexander Kutikov, Robert Uzzo. REGIONALIZATION OF RENAL SURGERY: IMPACT OF HOSPITAL VOLUME ON UTILIZATION OF PARTIAL NEPHRECTOMY. *Journal of Urology*. 2012;187(4S):e174-175.
20. Monn MF, Bahler CD, Flack CK, Dube HT, Sundaram CP. The impact of hospital volume on postoperative complications following robot-assisted partial nephrectomy. *Journal of endourology / Endourological Society*. 2014;28(10):1231-1236.

21. Cooperberg MR, Modak S, Konety BR. Trends in regionalization of inpatient care for urological malignancies, 1988 to 2002. *The Journal of urology.* 2007;178(5):2103-2108; discussion 2108.
22. Birkmeyer NJ, Goodney PP, Stukel TA, Hillner BE, Birkmeyer JD. Do cancer centers designated by the National Cancer Institute have better surgical outcomes? *Cancer.* 2005;103(3):435-441.
23. Paulson EC, Mitra N, Sonnad S, et al. National Cancer Institute designation predicts improved outcomes in colorectal cancer surgery. *Annals of surgery.* 2008;248(4):675-686.
24. Bilimoria KY, Talamonti MS, Wayne JD, et al. Effect of hospital type and volume on lymph node evaluation for gastric and pancreatic cancer. *Archives of surgery.* 2008;143(7):671-678; discussion 678.
25. Emanuel EJ, Wendler D, Grady C. What makes clinical research ethical? *Jama.* 2000;283(20):2701-2711.
26. Nuremberg Military T. The Nuremberg Code. *Jama.* 1996;276(20): 1691.
27. Assembly WMAG. WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. 1964; http://www.wma.net/en/30publications/10policies/b3/. Accessed 12/1/ 2014, 2014.
28. Protection of human subjects; Belmont Report: notice of report for public comment. *Federal register.* 1979;44(76):23191-23197.
29. Ghooi RB. The Nuremberg Code-A critique. *Perspectives in clinical research.* 2011;2(2):72-76.
30. Millum J, Wendler D, Emanuel EJ. The 50th anniversary of the Declaration of Helsinki: progress but many remaining challenges. *Jama.* 2013;310(20):2143-2144.
31. Volpe A, Finelli A, Gill IS, et al. Rationale for percutaneous biopsy and histologic characterisation of renal tumours. *European urology.* 2012;62(3):491-504.
32. Halverson SJ, Kunju LP, Bhalla R, et al. Accuracy of determining small renal mass management with risk stratified biopsies: confirmation by final pathology. *The Journal of urology.* 2013;189(2):441-446.
33. Peppercorn J, Shapira I, Collyar D, et al. Ethics of mandatory research biopsy for correlative end points within clinical trials in oncology. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2010;28(15):2635-2640.
34. Overman MJ, Modak J, Kopetz S, et al. Use of research biopsies in clinical trials: are risks and benefits adequately discussed? *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2013;31(1):17-22.
35. Olson EM, Lin NU, Krop IE, Winer EP. The ethical use of mandatory research biopsies. *Nature reviews. Clinical oncology.* 2011;8(10):620-625.
36. Peppercorn J. Toward improved understanding of the ethical and clinical issues surrounding mandatory research biopsies. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2013;31(1):1-2.
37. 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.
38. Escudier B, Bellmunt J, Negrier S, et al. Phase III trial of bevacizumab plus interferon alfa-2a in patients with metastatic renal cell carcinoma (AVOREN): final analysis of overall survival. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2010;28(13): 2144-2150.
39. Rini BI, Halabi S, Rosenberg JE, et al. Phase III trial of bevacizumab plus interferon alfa versus interferon alfa monotherapy in patients with metastatic renal cell carcinoma: final results of CALGB 90206. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2010;28(13):2137-2143.
40. 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.
41. Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2010;28(6):1061-1068.
42. Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. *The New England Journal of Medicine.* 2007;356 (2):125-134.
43. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *The New England journal of medicine.* 2007;356(2):115-124.
44. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *The New England journal of medicine.* 2007;356(22):2271-2281.
45. Singer EA, Gupta GN, Marchalik D, Srinivasan R. Evolving therapeutic targets in renal cell carcinoma. *Current opinion in oncology.* 2013;25(3):273-280.
46. Emanuel EJ, Miller FG. The ethics of placebo-controlled trials—a middle ground. *The New England journal of medicine.* 2001;345(12):915-919.
47. Temple R, Ellenberg SS. Placebo-controlled trials and active-control trials in the evaluation of new treatments. Part 1: ethical and scientific issues. *Annals of internal medicine.* 2000;133(6):455-463.
48. Daugherty CK, Ratain MJ, Emanuel EJ, Farrell AT, Schilsky RL. Ethical, scientific, and regulatory perspectives regarding the use of placebos in cancer clinical trials. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2008;26(8):1371-1378.
49. Smith TJ, Temin S, Alesi ER, et al. American Society of Clinical Oncology provisional clinical opinion: the integration of palliative care into standard oncology care. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2012;30(8):880-887.
50. Peppercorn JM, Smith TJ, Helft PR, et al. American society of clinical oncology statement: toward individualized care for patients with advanced cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2011;29(6):755-760.
51. Joffe S, Miller FG. Ethics of cancer clinical trials in low-resource settings. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2014;32(28):3192-3196. KCJ

Legend
NHS: National Health Service
BAUS: British Association of Urological Surgeons
NCI: National Cancer Institute
TKI: Tyrosine kinase inhibitor

EDITOR'S MEMO *(continued from page 6)*

Finding the "Devil in the Details" in Managing Kidney Cancer

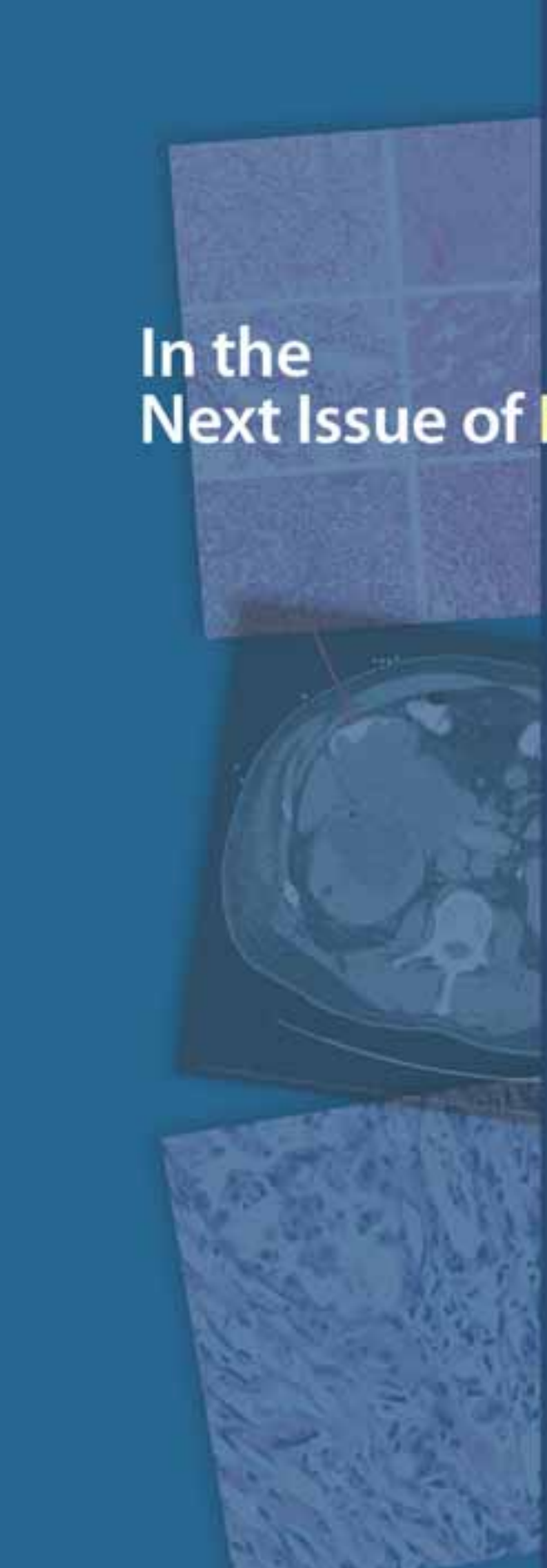
ne of the more intriguing idioms is the expression, "the devil is in the details," which means that mistakes are usually made in the small details of a project. Usually it is a cautionary tale, involving the need to pay attention to avoid failure, an expression of the concept that many things seem straightforward on the surface, but difficulties, problems, and obstacles are later discovered while trying to implement or execute a task or plan.

Although it seems somewhat of a cliché these days, it still has universal application, including our oncology practices where the details and nuances of our relationships with patients, their families and other health care

vessels. Pazopanib (800mg QD) was administered for 8-16 weeks with repeat imaging at completion of therapy, followed by surgery. Twenty-five patients enrolled with median tumor size 7.3cm and median RENAL score of 11; 80% of index lesions were high complexity, and 56% of patients had a solitary kidney. Patients received a median 8 weeks of
pazopanib; median interval from treatment start to surgery was 10.6 weeks. RENAL score decreased in 71% of tumors and 92% of patients experienced reduction in tumor volume; 6 of 13 patients for whom PN was not possible at baseline were able to undergo PN after treatment. The mean parenchymal volume that could be saved with surgery increased from estimated 107cc to 173cc (P=0.0015). Five patients developed urine leak managed conservatively, and 7 received a transfusion, one of whom required embolization.
Conclusion: Neoadjuvant pazopanib resulted in downsizing of localized RCC, allowing improved preservation of renal parenchyma, and enabling PN in a select subset of patients who would otherwise require radical nephrectomy.

Targeting survivin inhibits renal cell carcinoma progression and enhances the activity of temsirolimus. Carew JS, Espitia CM, Zhao W, et al. *Mol Cancer Ther*. 2015 Mar 25. pii: molcanther.1036.2014. [Epub ahead of print]
Summary: This paper investigated the roles of the anti-apoptotic factor survivin in RCC tumor progression, resistance to mammalian target of rapamycin (mTOR) inhibitors, and evaluated the therapeutic activity of the survivin suppressant YM155 in RCC models. Survivin expression levels were significantly higher in RCC cell lines compared to normal renal cells. Stable targeted knockdown of survivin completely abrogated the ability of 786-O RCC tumors to grow in mice, thus demonstrating its importance as a regulator of RCC tumorigenesis. Treatment with the mTOR inhibitor temsirolimus partially diminished survivin levels and this effect was augmented by the addition of YM155. Further analyses revealed that, in accordance with their combined anti-survivin effects, YM155 significantly improved the anticancer activity of temsirolimus in a panel of RCC cell lines in vitro and in xenograft models in vivo. Similar to pharmacological inhibition of survivin, shRNA-mediated silencing of survivin expression not only inhibited RCC tumor growth, but also significantly sensitized RCC cells to temsirolimus therapy. The effectiveness of this dual survivin/mTOR inhibition strategy was mediated by a potent decrease in survivin levels and corresponding induction of apoptosis.
Conclusion: Survivin inhibition as a novel approach to improve RCC therapy that warrants further investigation.

Survival, durable response, and long-term safety in patients with previously treated advanced renal cell carcinoma receiving nivolumab. McDermott DF, Drake CG, Sznol M, et al. *J Clin Oncol*. 2015 Mar 30. pii: JCO.2014.58. 1041. [Epub ahead of print]
Summary: Nivolumab mediates tumor regression in a portion of patients with advanced treatment-refractory solid tumors. In a phase 1 study 34 patients with previously treated advanced RCC, enrolled between 2008 and 2012, received intravenous nivolumab (1 or 10 mg/kg) in an outpatient setting once every two weeks for up to 96 weeks. Ten patients (29%) achieved objective responses (according to RECIST [version 1.0]), with median response duration of 12.9 months; nine additional patients (27%) demonstrated stable disease lasting > 24 weeks. Three of five patients who stopped treatment while in response continued to respond for ≥ 45 weeks. Median overall survival in all patients (71% with two to five prior systemic therapies) was 22.4 months; 1-, 2-, and 3-year survival rates were 71%, 48%, and 44%, respectively. Grade 3 to 4 treatment-related adverse events occurred in 18% of patients; all were reversible.
Conclusion: Patients with advanced treatment-refractory RCC treated with nivolumab demonstrated durable responses that in some responders persisted after drug discontinuation. Overall survival is encouraging, and toxicities were generally manageable. Ongoing randomized clinical trials will further assess the impact of nivolumab on overall survival in patients with advanced RCC. KCJ



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- the pitfalls and limitations of various imaging techniques
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