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
6.7 months median PFS with INLYTA vs 4.7 months with sorafenib

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

Important Safety Information

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

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

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

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

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

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

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

Monitor for **proteinuria** before initiation of, and periodically throughout, treatment. For moderate to severe proteinuria, reduce the dose or temporarily interrupt treatment.
Inlyta.
axitinib
3mg ext3mg tablets

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

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

EVIDENCE

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

INLYTA was the 1st agent to demonstrate SUPERIOR EFFICACY to sorafenib

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

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

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

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

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

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

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

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

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

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

Please see brief summary on the following pages.
INLYTA® (AXITINIB) 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 or progression on previous systemic therapy.

DOSE AND ADMINISTRATION

Recommended Dosing. The recommended starting oral dose of INLYTA is 5 mg twice daily. Administer INLYTA with food 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 candidates for receiving anti-hypertensive therapy. 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.

Dose modification should be considered in the management of some adverse reactions which 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 the dose needs to be reduced further, the recommended dose is 2 mg twice daily.

INLYTA (axitinib) is supplied as white, round tablets containing 1 mg INLYTA (axitinib) intended for oral administration. Each tablet contains 1 mg of INLYTA (axitinib) and 1 mg of microcrystalline cellulose. The tablets are scored for easy breakage into halves.

INLYTA is supplied in bottles of 10 tablets and 100 tablets.

INLYTA (axitinib) tablets are supplied as follows:

- Tablets—1 mg INLYTA (axitinib) tablets—10 tablets/bottle, 100 tablets/bottle

ADVERSE REACTIONS

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 33/359 patients (9%) 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.

INLYTA is associated with a higher incidence and severity of hypertension compared to sorafenib. INLYTA 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 dose of INLYTA. Do not reduce the dose of INLYTA to <5 mg twice daily.

INLYTA is associated with a higher incidence of RPLS, proteinuria, elevation of liver enzymes, and fetal development compared to sorafenib. These effects were reported in both INLYTA and sorafenib clinical trials. Women of childbearing potential should be advised to avoid becoming pregnant while receiving INLYTA.

INLYTA should be interrupted, patients receiving anti-hypertensive medications should be monitored for hypotension.

Arterial Thromboembolic Events. In a controlled clinical study with INLYTA for the treatment of patients with RCC, arterial thromboembolic events were reported in 16/359 patients (4%) receiving INLYTA and 20/355 patients (6%) receiving sorafenib. 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. There were 11 additional reports of arterial thromboembolic events (including transient ischemic attack, cerebrovascular accident, myocardial infarction, and retinal artery occlusion) reported in patients receiving INLYTA.

INLYTA is associated with a higher incidence and severity of arterial thromboembolic events compared to sorafenib. INLYTA should be interrupted, patients receiving anti-platelet therapy or anti-coagulation should be monitored for bleeding complications.

Hypothyroidism. Hypothyroidism was reported in 69/359 patients (19%) receiving INLYTA and 29/355 patients (8%) receiving sorafenib. Thyroid dysfunction should be monitored in patients receiving INLYTA.

Optic Neuropathy. Optic neuropathy is a dose-limiting adverse reaction observed in INLYTA clinical studies. Hypothyroidism is required in patients receiving INLYTA.

Hematology Abnormalities. Hematological abnormalities were reported in patients treated with INLYTA. Significant abnormalities were reported in patients receiving INLYTA and not receiving sorafenib. Platelet count was decreased in INLYTA patients compared to sorafenib patients.

Gastrointestinal (GI) Abnormalities. GI abnormalities were reported in 435/359 patients (1%) receiving sorafenib. GI abnormalities were reported in 2/359 patients (<1%) receiving INLYTA and none of the patients receiving sorafenib.

INLYTA is associated with a higher incidence of gastrointestinal (GI) adverse reactions compared to sorafenib. INLYTA should be interrupted if GI toxicity occurs.

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. INLYTA is associated with reversible posterior leukoencephalopathy syndrome (RPLS) which can occur at any time during treatment. Clinical trials with INLYTA showed RPLS was reported in 3/359 patients (1%) receiving INLYTA and none of the patients receiving sorafenib. There were 11 additional reports of RPLS in patients receiving索拉非尼.

INLYTA is associated with a higher incidence and severity of RPLS compared to sorafenib. INLYTA should be interrupted if RPLS occurs and not restarted until symptoms resolve.

INLYTA is associated with a higher incidence and severity of arterial thromboembolic events compared to sorafenib. INLYTA should be interrupted, patients receiving anti-platelet therapy or anti-coagulation should be monitored for bleeding complications.

INLYTA is associated with a higher incidence and severity of arterial thromboembolic events compared to sorafenib. INLYTA should be interrupted, patients receiving anti-platelet therapy or anti-coagulation should be monitored for bleeding complications.

Ocular Toxicity. INLYTA is associated with an increased incidence of ocular toxicity compared to sorafenib. INLYTA patients may have an increased risk of uveitis, retinitispigmentosa, and visual acuity loss.

INLYTA is associated with a higher incidence and severity of ocular toxicity compared to sorafenib. INLYTA should be interrupted, patients receiving anti-platelet therapy or anti-coagulation should be monitored for visual acuity loss.

INLYTA is associated with a higher incidence and severity of ocular toxicity compared to sorafenib. INLYTA should be interrupted, patients receiving anti-platelet therapy or anti-coagulation should be monitored for visual acuity loss.
Selected adverse reactions (all grades) that were reported in <10% of patients treated with INLYTA included: anemia (9%), allergic reaction (9%), abdominal pain (8%), dyspepsia (8%), hepatotoxicity (7%), hematuria (5%), hypothyroidism (5%), and hypercalcemia (4%).

Table 2. Laboratory Abnormalities Occurring in ≥10% of Patients Who Received INLYTA or Sorafenib

**Laboratory Abnormality** | **INLYTA** | **N** | **Grade 3** | **Grade 4** | **Sorafenib** | **N** | **Grade 3** | **Grade 4**
--- | --- | --- | --- | --- | --- | --- | --- | ---
**Hematology** | | | | | | | | |
Anemia | 436 | 36 | 1 | 306 | 25 | 4
Platelets decreased | 317 | 33 | 1 | 309 | 36 | 4
White blood cells decreased | 312 | 15 | 1 | 310 | 14 | 0
**Chemistry** | | | | | | | | |
Creatinine increased | 336 | 55 | 0 | 318 | 41 | 1
Bicarbonate decreased | 321 | 44 | 0 | 313 | 40 | 0
Hyponatremia | 318 | 46 | 1 | 315 | 16 | 1
Amylase increased | 328 | 52 | 0 | 319 | 33 | 2
AST increased | 331 | 20 | 0 | 311 | 25 | 1
**ONCOLOGY**

**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 hypotension. 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 toxicity studies, findings in the male reproductive tract were observed in the testes/epididymis (atrophy and/or degeneration, decreased numbers of germinal cells, hypospermatia 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).

**PREGNANCY**

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

**Pregnancy.**

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

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

**Rx only**

Issued: September 2013


**mRCC-metastatic renal cell carcinoma; OQR-objective response rate; OS-overall survival; PS-progression-free survival.**
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.

Medical Advisory Board
Michael B. Atkins, MD
Deputy Director
Lombardi Comprehensive Cancer Center
Professor of Oncology and Medicine,
Georgetown University Medical Center
Washington, DC

Ronald M. Bukowski, MD
Emeritus Staff & Consultant
CCF Taussig Cancer Center
Professor of Medicine
C CF Lerner College of Medicine of CW RU
Cleveland, Ohio

Robert J. Motzer, MD
Attending Physician
Memorial Sloan-Kettering Cancer Center
New York, NY

Christopher G. Wood, MD, FACS
Attending Physician
Samuel Oschin Comprehensive Cancer Institute
Los Angeles, California

Nurse Advisory Board
Nancy Moldawer, RN, MSN
Nursing Director
Cedars-Sinai Medical Center
Los Angeles, California

Laura Wood, RN, MSN, OCN
Renal Cancer Research Coordinator
Cleveland Clinic Taussig Cancer Center
Cleveland, Ohio

Patient Advocate
William P. Bro
Chief Executive Officer
Kidney Cancer Association

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

Finding the “Devil in the Details” in Managing Kidney Cancer

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)
Peer Review and Editing

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

Conflict of Interest

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

Manuscript Preparation

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

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

References

All submissions should have references that are referred to in the text by superscripted numbers and that conform to AMA style.

Example:


Copyright

Manuscripts and accompanying material are accepted for exclusive publication in the Kidney Cancer Journal. None of the contents may be reproduced without permission of the Kidney Cancer Journal. To request permission, please contact Stu Chapman, Executive Editor, (516) 356-5006; email: stulink@aol.com.

**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.


**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. The 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.


**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.


**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/1.73m² or PN high risk due to high complexity (RENAL=10-12) or tumor adjacent to hilar vessels. (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 conveys 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, sunitinib, or placebo, and treated up to 1 year. 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 sunitinib 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/m² had a longer overall survival compared with those with BMI <25 kg/m² (23.4 months vs 14.5 months; HR, 0.830; P = .0008). Patients with BMI ≥25 kg/m² 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, PA. PT2385 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 community 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."
Ethical Issues in the Management of Renal Cell Carcinoma: Creating a Framework for Resolving Complex Questions

Parth K. Modi, MD  
Resident  
Division of Urology  
Rutgers Robert Wood Johnson Medical School  
New Brunswick, New Jersey

Eric A. Singer, MD, MA  
Assistant Professor of Surgery  
Director, Kidney Cancer Program  
Section of Urologic Oncology  
Rutgers Cancer Institute of New Jersey  
Director, Distinction in Bioethics Program  
Rutgers Robert Wood Johnson Medical School  
New Brunswick, New Jersey

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 carcinoma2 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 volume5 and objective ratings of surgeon skill6 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 discussion3,8 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 Oakley10 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.

Corresponding Author: Eric A. Singer, MD, MA Rutgers Cancer Institute of New Jersey, 195 Little Albany Street, New Brunswick, NJ 08903. Email: eric.singer@rutgers.edu. Telephone: (732) 235-2043
Save the Date

Fourteenth International Kidney Cancer Symposium

November 6-7, 2015
Marriott Miami Biscayne Bay, Miami, Florida

KidneyCancer.com

www.kidneycancersymposium.com

For more information about the Kidney Cancer Association and about the Fourteenth International Kidney Cancer Symposium in Miami go to:

www.kidneycancer.com
www.kidneycancersymposium.com
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 high-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 Moni 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 nodes24 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 research25 (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 al33 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 cate-
Categories: clinical biopsy, research biopsy for correlative science, and research biopsy for integral biomarker research. 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.

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)

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

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Explanation</th>
<th>Justifying Ethical Values</th>
<th>Expertise for Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Social or scientific value</td>
<td>Evaluation of a treatment, intervention, or theory that will improve health and well-being or increase knowledge</td>
<td>Scarce resources and nonexploitation</td>
<td>Scientific knowledge; citizen’s understanding of social priorities</td>
</tr>
<tr>
<td>Scientific validity</td>
<td>Use of accepted scientific principles and methods, including statistical techniques, to produce reliable and valid data</td>
<td>Scarce resources and nonexploitation</td>
<td>Scientific and statistical knowledge; knowledge of condition and population to assess feasibility</td>
</tr>
<tr>
<td>Fair subject selection</td>
<td>Selection of subjects so that stigmatized and vulnerable individuals are not targeted for risky research and the rich and socially powerful not favored for potentially beneficial research</td>
<td>Justice</td>
<td>Scientific knowledge; ethical and legal knowledge</td>
</tr>
<tr>
<td>Favorable risk-benefit ratio</td>
<td>Minimization of risks; enhancement of potential benefits; risks to the subject are proportionate to the benefits to the subject and society</td>
<td>Nonmaleficence, beneficence, and nonexploitation</td>
<td>Scientific knowledge; citizen’s understanding of social values</td>
</tr>
<tr>
<td>Independent review</td>
<td>Review of the design of the research trial, its proposed subject population, and risk-benefit ratio by individuals unaffiliated with the research</td>
<td>Respect for subject autonomy</td>
<td>Scientific knowledge; ethical and legal knowledge</td>
</tr>
<tr>
<td>Informed consent</td>
<td>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 voluntary decision whether to enroll and continue to participate</td>
<td>Respect for subject autonomy</td>
<td>Scientific knowledge; ethical and legal knowledge</td>
</tr>
</tbody>
</table>
| Respect for potential and enrolled subjects | 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 |

Reproduced from Emanuel et al\textsuperscript{25} with permission.
Emanuel and Miller have compared the merits of placebo-control and active-control trials. 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. Furthermore, proponents claim, even if a treatment isn’t better than an existing therapy, it may have fewer side effects or less cost. 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. 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. 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. The active-control argument also has flaws, they argue, as it creates a false dichotomy between rigorous science and ethical research. (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. 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. 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. Similarly, in research involving non-serious ailments, where the chance for harm or discomfort is negligible, placebo-control is ethical.

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. If these criteria are met, they argue, the use of placebo control should be evaluated for potential risks of death, disability, harm or discomfort. Only in the absence of a substantial difference in these risks can a placebo control ethically be used.

While previous revisions of the Declaration of Helsinki prohibited the use of placebo when any active treatment existed for a condition, 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.”

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. 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. In this setting, there may be equipoise, or uncertainty, when comparing placebo with best supportive care to these active control options. Daugherty et al also propose several methodological strategies to minimize the potential harms of placebo. First, the use of clinically relevant surrogate endpoints instead of survival can shorten the duration of a study and therefore decrease exposure and risk of harm to subjects. 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.

A recent example of the use of placebo in clinical kidney cancer trials is the 2010 Phase III trial of pazopanib in

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

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Target</th>
<th>Treatment Line</th>
<th>Comparison Arm</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axitinib</td>
<td>VEGFR</td>
<td>Second-Line</td>
<td>Sorafenib</td>
<td>PFS</td>
</tr>
<tr>
<td>Bevacizumab + IFN-α (AVOREN)</td>
<td>VEGF</td>
<td>First-line</td>
<td>Placebo + IFN-α</td>
<td>OS</td>
</tr>
<tr>
<td>Bevacizumab + IFN-α (CALGB)</td>
<td>VEGF</td>
<td>First-line</td>
<td>IFN-α</td>
<td>OS</td>
</tr>
<tr>
<td>Everolimus</td>
<td>mTOR</td>
<td>VEGFR Failure</td>
<td>Placebo</td>
<td>PFS</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>VEGFR</td>
<td>First-line or Cytokine Failure</td>
<td>Placebo</td>
<td>PFS</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>VEGFR</td>
<td>Cytokine Failure</td>
<td>Placebo</td>
<td>OS</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>VEGFR</td>
<td>First-line</td>
<td>IFN-α</td>
<td>PFS</td>
</tr>
<tr>
<td>Temsirolimus</td>
<td>mTOR</td>
<td>First-line</td>
<td>IFN-α</td>
<td>OS</td>
</tr>
</tbody>
</table>

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 with permission.
metastatic and locally advanced kidney cancer.\textsuperscript{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.”\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.”\textsuperscript{51}

The high burden of cancer in the developing world highlights the need for clinical research in low-resource settings.\textsuperscript{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.

\section*{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.

\section*{Funding}

This work is supported by a grant from the National Cancer Institute (P30CA077270).

\section*{References}

ence has been shown to independently predict patient outcomes. So the question arises: to what extent are physicians obligated to disclose their experience? Yes, the devil is in the details. I urge you to discover them by reading this article covering a broad range of ethical issues in renal cancer.

These are troubling and significant questions and in the case of medical ethics have even been described as dilemmas. Since the devil is in the details, we must, by the very nature of our practice be concerned with confronting difficulties, problems, and obstacles on a routine basis and preventing these details from complicating the course of care at a much later time. It is a challenge that reflects the essence of providing high quality value based care.

Robert A. Figlin, MD
Editor-in-Chief
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.


**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.


**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.
A comprehensive report and analysis on risk stratification of the local renal mass
• a review by three authors at the Johns Hopkins University School of Medicine
• emerging data on the risk/benefit of renal mass biopsy
• the latest results concerning intra-tumor heterogeneity and implications of determining malignant potential compiled from recent reports and databases
• the pitfalls and limitations of various imaging techniques
• results on application of the nephro-metry score and current nomograms
• a preview of nuclear imaging and its potential applications

Highlights from the 2015 meeting of the American Society of Clinical Oncology
• noteworthy abstracts with possible translational impact
• news from the symposia, panel discussions and oral sessions on kidney cancer
Kidney Cancer Journal will make this address one of your favorite educational sites for in-depth information on the diagnosis and treatment of renal cell carcinoma.

Visit the journal’s website frequently for:

- Regular News Alerts on late-breaking developments in the field.
- New CME offerings and how to access them online.
- The complete archive of past issues of the KCJ.
- Related publications on kidney cancer.