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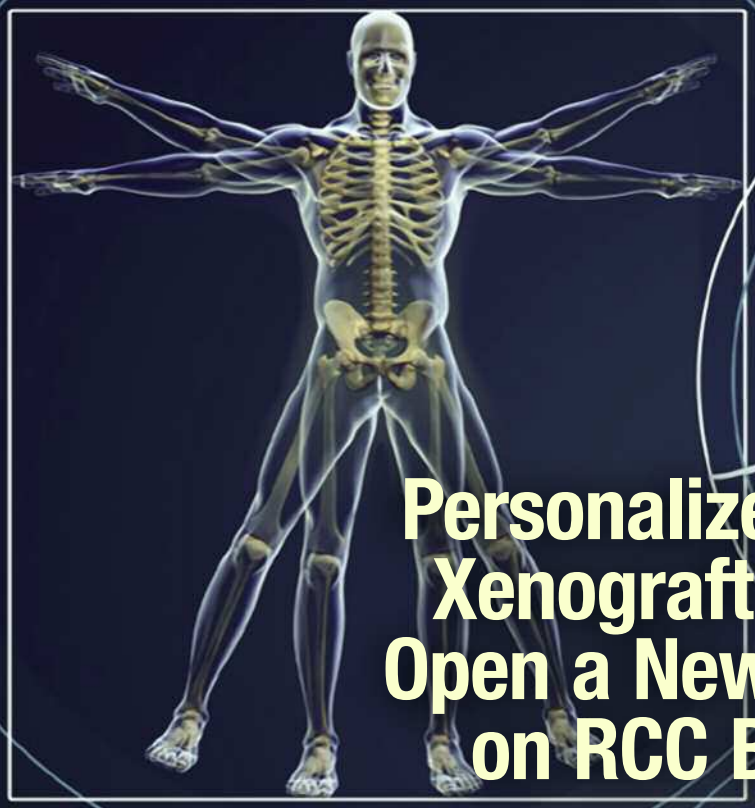
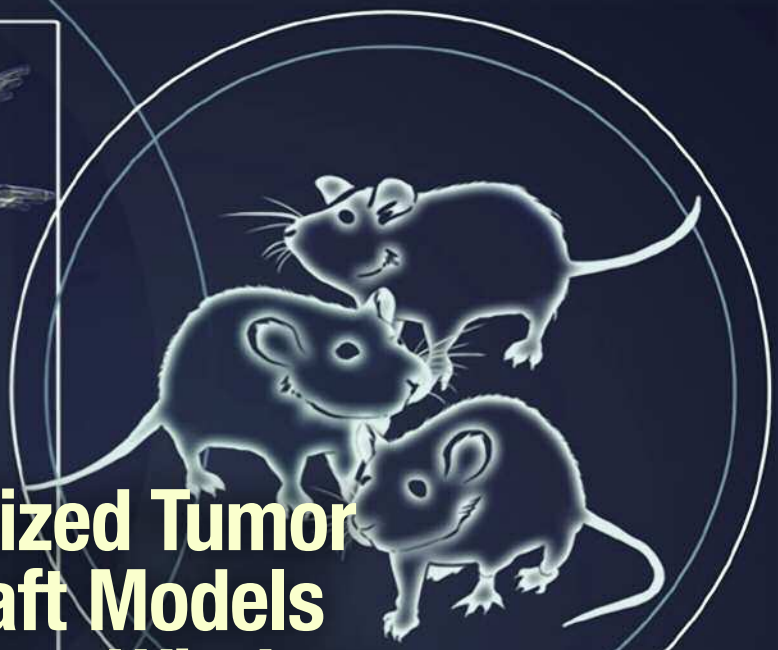
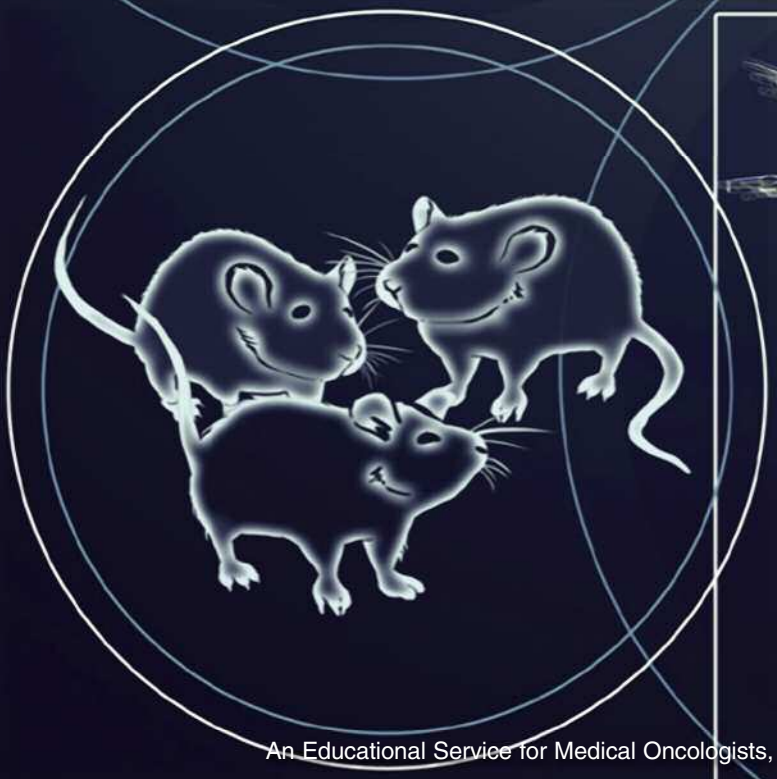
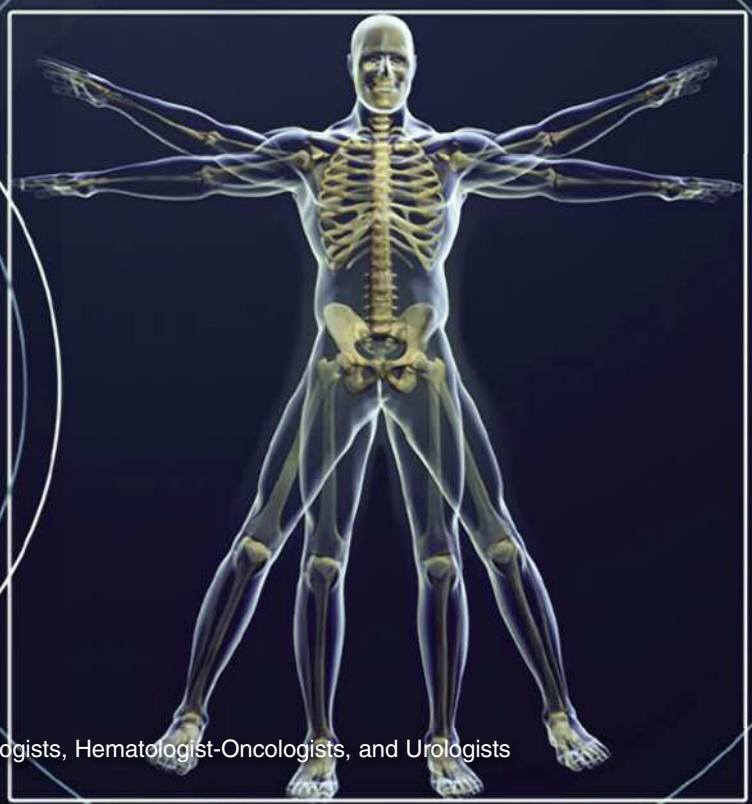




Personalized Tumor Xenograft Models Open a New Window on RCC Biology





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

6.7 months median PFS with INLYTA vs 4.7 months with sorafenib

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

Important Safety Information

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

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

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

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

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

Stop INLYTA at least 24 hours prior to scheduled surgery.

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

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

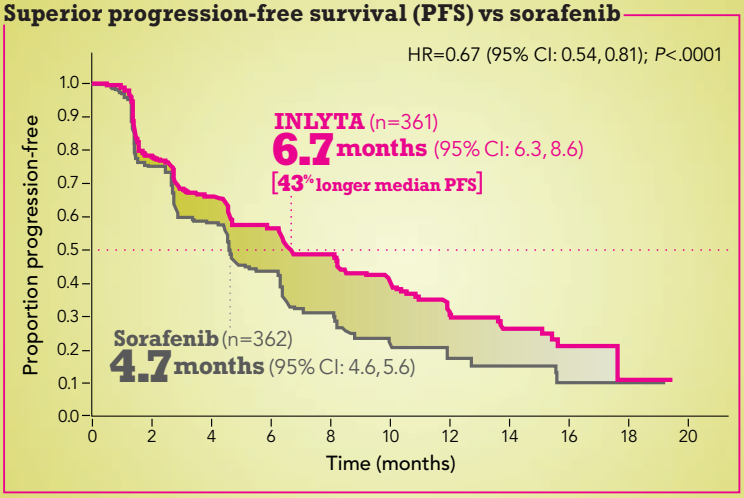
INLYTA®

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

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

IT MATTERS.

Superior progression-free survival (PFS) vs sorafenib



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

More than doubled objective response rate[1]

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

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

- Preclinical activity does not necessarily correlate with clinical outcomes

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

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

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

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

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

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

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

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

Please see brief summary on the following page.

Inlyta™
axitinib 1mg and 5mg tablets

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

INLYTA® (AXITINIB) TABLETS FOR ORAL ADMINISTRATION

Initial U.S. Approval: 2012

Brief Summary of Prescribing Information

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

DOSAGE AND ADMINISTRATION

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

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

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

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

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

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

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

DOSAGE FORMS AND STRENGTHS

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

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

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DRUG INTERACTIONS

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

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

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

USE IN SPECIFIC POPULATIONS

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

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

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

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

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

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

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

No dosage adjustment is required in elderly patients.

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

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

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

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

OVERDOSAGE

There is no specific treatment for INLYTA overdose.

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

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

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

NONCLINICAL TOXICOLOGY

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

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

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

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

PATIENT COUNSELING INFORMATION

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

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

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

Rx only

Issued: February 2012

Reference: 1. Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. *Lancet.* 2011;378(9807):1931-1939.

About the Cover
Xenograft tumor models in mice are providing a new avenue to understanding the biology of renal cell carcinoma. The combination of images in a conceptual framework, including the drawing by Leonardo da Vinci of Vitruvian Man, evokes this new understanding in a broader context of art and scientific research. (Images courtesy of Livio Trusolino, MD, Institute for Cancer Research, Candiolo, Italy)

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KCJ GUEST EDITOR'S MEMO

Are We There Yet? No, But Buckle Up, New Xenograft Tumor Models Are Getting Ready to Take Off


Eric Jonash, MD

One of the challenges facing the renal cell carcinoma (RCC) community involves development of an effective mouse model of the disease, one that can retain histological, immunophenotypic, and genetic features of tumors in patients. Until now, available models were based on subcutaneous implantation of passaged and immortalized human RCC cell lines in immunodeficient recipient mice. These models are not ideal—cancer cells continuously cultured in vitro acquire genetic alterations not found in the original tumor, according to our report in this issue of the journal. In addition, these cell lines lack the heterogeneity that characterizes RCC in the human population.

Our report reviews the development of a panel of well-characterized primary tumor xenografts of RCC, obtained by implanting intact human cancer tissues orthotopically in immunodeficient mice. Although the results need to be replicated, we are seeing promising signs of what could foster a deeper understanding of RCC carcinogenesis. These models could yield important insights for preclinical and translational applications. The most exciting aspect of these new studies is the way in which xenograft models mimic the behavior of the patient tumor from which it was derived. The xenograft model can be used to assess resistance to various targeted therapies and ultimately, may be used to determine therapeutic strategies.

Are we there yet? So goes the refrain of an impatient youngster waiting for his or her arrival at a destination. We, too, are awaiting an arrival at a distant destination—when "clinical co-trials" in such xenograft models can predict therapy responsiveness of their human RCC patient donors. My colleagues at MD Anderson Cancer Center, Christopher G. Wood, MD, and Jose A. Karam, MD, present a comprehensive overview of current and earlier studies and hint at what the future may bring in terms of xenograft models on a much larger scale. It is far too premature to speculate on when these visions could materialize but they are tantalizing to contemplate. Imagine what it would be like if these "co-clinical" trials could be coordinated on a grand scale to accrue and compile extensive data regarding the genetic profile of tumors before and after treatment?

The concept is futuristic but, given the progress made in studies like the one published last year by Drs. Wood and Karum, perhaps not as far-fetched as one would suspect. As the use and understanding of these models proliferates, co-clinical bioinformatics centers could be created where all data from xenograft models are collected and compiled, compared, and cross-referenced to provide a comprehensive overview of how the response from preclinical trials in mice can assist in the design of clinical trials and inform the clinic regarding stratification of patients,

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KCJ JOURNAL CLUB

Essential Peer-Reviewed Reading in Kidney Cancer

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

Markers predict benefit of pazopanib

Prognostic or predictive plasma cytokines and angiogenic factors for patients treated with pazopanib for metastatic renal-cell cancer: a retrospective analysis of phase 2 and phase 3 trials. Tran HT, Liu Y, Zurita AJ, et al. *Lancet Oncol*; 2012:827-837.

Summary: No validated biomarkers are available for prediction of clinical outcome in metastatic renal cell carcinoma. This report assessed the prognostic and predictive associations of pretreatment plasma concentrations of cytokine and angiogenic factors (CAFs) with data from a phase 2 and a phase 3 trial of pazopanib treatment. The authors screened 17 CAFs in 129 patients who had the greatest or least tumor shrinkage in a phase 2 trial of 215 patients treated with pazopanib. They confirmed associations of candidate CAFs (those identified in the screening and from previous studies) with tumor response and progression-free survival (PFS) in 215 patients from this phase 2 trial with an independent analytical platform. The study validated confirmed markers in 344 patients from a randomized, placebo-controlled, phase 3 clinical study of pazopanib. Five candidate markers emerged from initial screening—interleukin 6, interleukin 8, hepatocyte growth factor (HGF), tissue inhibitor of metalloproteinases (TIMP)-1, and E-selectin. Confirmatory analyses identified associations of interleukin 6, interleukin 8, VEGF, osteopontin, E-selectin, and HGF with continuous tumor shrinkage or PFS in patients treated with pazopanib. In the validation set of samples from the phase 3 trial, patients treated with pazopanib who had high concentrations (relative to median) of interleukin 8 (P=0.006), osteopontin (P=0.0004), HGF (P=0·010), and TIMP-1 (P=0.006) had shorter PFS than did those with low concentrations. In the placebo group, high concentrations of interleukin 6 (P<0.0001), interleukin 8 (P=0.002), and osteopontin (P<0.0001) were all prognostically associated with shorter PFS. These factors were stronger prognostic markers than were standard clinical classifications (Eastern Cooperative Oncology Group, Memorial Sloan-Kettering Cancer Center, and Heng criteria). High concentrations of interleukin 6 were predictive of improved relative PFS benefit from pazopanib compared with placebo (pinteraction=0.009); standard clinical classifications were not predictive of PFS benefit.

Conclusion: CAF profiles could provide prognostic information beyond that of standard clinical classification and identify markers predictive of pazopanib benefit in patients with metastatic renal-cell carcinoma. Further studies of the predictive effects of these markers in different populations and with different drugs (eg, mTOR inhibitors) are warranted.

(continued on page 68)

Update focuses on key genomic and molecular features of RCC

State of the science: an update on renal cell carcinoma. Jonasch E. Futreal PA, Davis IJ, et al. *Mol Cancer Res*. 2012;10:859-880.

Summary: Several major genomic and mechanistic discoveries are altering our core understanding of this multitude of cancers, including several new rare subtypes of renal cancers. In this review, these new findings are examined and placed in the context of the well-established association of clear cell RCC (ccRCC) with mutations in the von Hippel-Lindau (VHL) gene and resultant aberrant hypoxia inducible factor (HIF) signaling. The impact of novel ccRCC-associated genetic lesions on chromatin remodeling and epigenetic regulation is explored. The effects of VHL mutation on primary ciliary function, extracellular matrix homeostasis, and tumor metabolism are discussed. Studies of VHL proteostasis, with the goal of harnessing the proteostatic machinery to refunctionalize mutant VHL, are reviewed. Translational efforts using molecular tools to elucidate discriminating features of ccRCC tumors and develop improved prognostic and predictive algorithms are presented, and new therapeutics arising from the earliest molecular discoveries in ccRCC are summarized.
Conclusion: By creating an integrated review of the key genomic and molecular biological disease characteristics of ccRCC and placing these data in the context of the evolving therapeutic landscape, these authors intend to facilitate interaction among basic, translational, and clinical researchers involved in the treatment of kidney cancer and accelerate progress toward its ultimate eradication.

Loss of protein could help reclassify RCC and its gene expression

BAP1 loss defines a new class of renal cell carcinoma. Peña-Llopis S, Vega-Rubin-de—Celis S, Liao A, et al. *Nat Genet*. 2012;10:751-759.

Summary: The molecular pathogenesis of renal cell carcinoma (RCC) is poorly understood. Whole-genome and exome sequencing followed by innovative tumorgraft analyses (to accurately determine mutant allele ratios) identified several putative two-hit tumor suppressor genes, including BAP1. The BAP1 protein, a nuclear deubiquitinase, is inactivated in 15% of clear cell RCCs. BAP1 cofractionates with and binds to HCF-1 in tumorgrafts. Mutations disrupting the HCF-1 binding motif impair BAP1-mediated suppression of cell proliferation but not deubiquitination of monoubiquitinated histone 2A lysine 119 (H2AK119ub1). BAP1 loss sensitizes RCC cells in vitro to genotoxic stress. Notably, mutations in BAP1 and PBRM1 anticorrelate in tumors, and combined loss of BAP1 and PBRM1 in a few RCCs was associated with rhabdoid features. BAP1 and PBRM1 regulate seemingly different gene expression programs, and BAP1 loss was associated with high tumor grade.
Conclusion: These results establish the foundation for an integrated pathological and molecular genetic classification of RCC, paving the way for subtype-specific treatments exploiting genetic vulnerabilities.

Sunitinib study highlights heterogeneity of non-clear cell RCC

A Phase 2 Trial of Sunitinib in Patients with Advanced Non-clear Cell Renal Cell Carcinoma. Tannir NM, Plimack E, Ng C, et al. *Eur Urol*. 2012:Jun 27 [Epub ahead of print].

Summary: This is a single-arm phase 2 trial with a two-stage design. Eligibility criteria included pathologically confirmed nccRCC or ccRCC with ≥20% sarcomatoid histology, performance status 0-2, measurable disease, a maximum of two prior systemic therapies, and no prior treatment with tyrosine kinase inhibitors directed against the vascular endothelial growth factor receptors. Patients received sunitinib 50mg daily on a 4-wk on, 2-wk off schedule. Primary end points were objective response rate (ORR) and progression-free survival (PFS). Secondary end points were safety and overall survival (OS). Fifty-seven patients were eligible (nccRCC histology: papillary, 27; chromophobe, 5; unclassified, 8; collecting duct or medullary carcinoma, 6; sarcomatoid, 7; and others, 4). Median PFS for 55 evaluable patients was 2.7 mo. Two patients with chromophobe and one patient with unclassified histology had a confirmed partial response (5% ORR). Median PFS for patients with papillary histology was 1.6 mo. Median PFS for patients with chromophobe histology was 12.7 mo. Median OS for all patients was 16.8 mo. Treatment-emergent adverse events were consistent with sunitinib's mechanism of action. The nonrandomized design and small number of patients are limitations of this study.
Conclusion: The differential response of chromophobe histology to sunitinib suggests a therapeutically relevant biological heterogeneity exists within nccRCC. The low ORR and short PFS with sunitinib in the other nccRCC subtypes underscore the need to enroll patients with these diverse tumors in clinical trials.

Intermitten dosing of sunitinib still remains standard of care

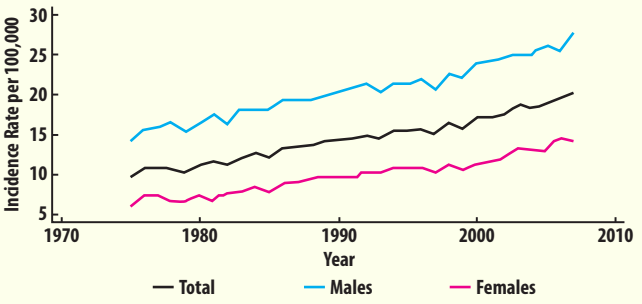
Randomized phase II trial of sunitinib on an intermittent versus continuous dosing schedule as first-line therapy for advanced renal cell carcinoma. Motzer RJ, Hutson TE, Olsen MR, et al. *J Clin Oncol*. 2012;30:1371-1377.

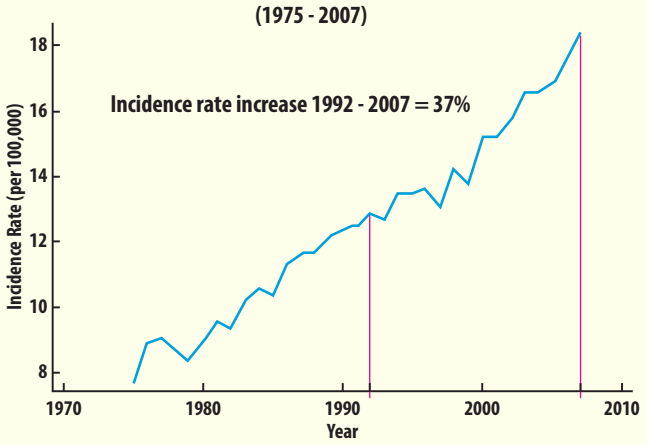
Summary: Sunitinib has shown antitumor activity with a manageable safety profile as metastatic renal cell carcinoma (RCC) treatment, when given by the standard intermittent schedule as well as a continuous daily dosing (CDD) schedule. A trial was conducted to compare the schedules. Patients with treatment-naive, clear cell advanced RCC were randomly assigned 1:1 to receive sunitinib 50 mg/d for 4 weeks followed by 2 weeks off treatment (schedule 4/2; n = 146) or 37.5 mg/d on the CDD schedule (n = 146) for up to 2 years. The primary end point was time to tumor progression. Median time to tumor progression was 9.9 months for schedule 4/2 and 7.1 months for the CDD schedule. No significant difference was observed in overall survival (23.1 v 23.5 months; $P = .615$), commonly reported adverse events, or patient-reported kidney cancer symptoms. Schedule 4/2 was statistically superior to CDD in time to deterioration, a composite end point of death, progression, and disease-related symptoms ($P = .034$).
Conclusion: There was no benefit in efficacy or safety for continuous dosing of sunitinib compared with the approved 50 mg/d dose on schedule 4/2. Given the numerically longer time to tumor progression with the approved 50 mg/d dose on schedule 4/2, adherence to this dose and schedule remains the treatment goal for patients with advanced RCC. KCJ

Tracking Trends From Web-based Sources, Translational Research, the FDA, and Patient Registries

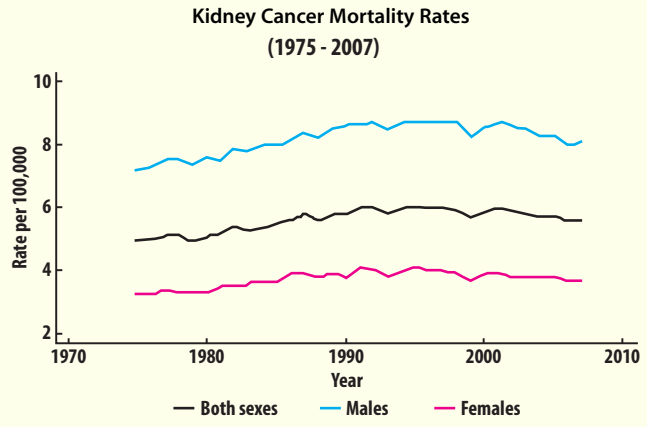
NCI Updates Trends on Incidence of Kidney Cancer

It is estimated that 64,770 men and women (40,250 men and 24,520 women) will be diagnosed with and 13,570 men and women will die of cancer of the kidney and renal pelvis in 2012.The following information is based on National Cancer Institute's SEER Cancer Statistics Review.





The kidney cancer incidence rate has been steadily increasing, probably due to increased imaging.



Although incidence rates have been rising, kidney cancer mortality rates have leveled off since 1990.

SEER is the Surveillance, Epidemiology and End Results (SEER) Program, a premier source for cancer statistics in the United States. It collects information on incidence, prevalence and survival from specific geographic areas representing 28% of the US population and compiles reports on all of these plus cancer mortality for the entire country.

Important Abstracts from ESMO identify treatment considerations

VIENNA, AUSTRIA—Presentations at the 2012 European Society of Medical Oncology highlighted new findings with the use of targeted therapy, particularly with regard to axitinib and sunitinib.

For axitinib, new results announced showed that:

- BP increased early with axitinib and was generally well-managed; 24-hr ambulatory BP measurements suggested there is no best time of day to measure BP. Rather, measuring at a consistent time of day in individual patients would provide the most useful data. Results from clinic and home monitoring appear consistent and both could be reliable in measuring BP and guiding axitinib therapy. This phase 2 study evaluating safety and efficacy of axitinib for treatment-naïve mRCC, prospectively characterized and compared BP measurements from clinic, home, and 24-hr ambulatory BP monitoring .
- In another study by Motzer et al, axitinib resulted in prolonged progression-free survival and similar overall survival (OS) compared with sorafenib for 2nd-line metastatic RCC. OS results and prognostic factors may be used in clinical trial design for novel agents in 2nd-line therapy. In this 12-week landmark analysis, median OS was significantly longer in the dBP ≥90 mmHg group (axitinib arm: 20.7 vs 12.9 mo, HR 0.725, $P = 0.014$; sorafenib arm: 20.9 vs 14.8 mo, HR 0.657, $P = 0.002$).

Study on markers for sunitinib efficacy showed that:

- Hypertension and hand-foot syndrome, and to a lesser degree asthenia/fatigue, may serve as independent biomarkers of sunitinib efficacy in mRCC patients. Providers who observe these AEs are therefore encouraged to continue sunitinib therapy, managing AEs with standard medical treatment with or without dose reduction as clinically indicated

The final multivariate models of associations between AEs and efficacy outcomes for metastatic RCC patients on Schedule 4/2 are summarized in the following table:

(continued on outside back cover)

Co-Clinical Trials, Using Personalized Tumor Xenograft Models, Usher in a New Paradigm to Understand Basic Biology of RCC and Response to Treatment

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Exploiting the mouse model of human kidney cancer to replicate a broad spectrum of mutational events in renal cell carcinoma and characterize the biology of these tumors, new studies are using xenografts to identify mechanisms of action, molecular correlates of response, and resistance to novel targeted therapies. Still investigational, these "co-clinical" trials could build a new platform of discovery in kidney cancer, possibly providing "real time" results in the animal that mimic the biology and expected responses and resistance of the tumor in a patient. Ultimately, if the results are validated, these personalized tumor xenograft models could help guide treatment decisions.

"Co-clinical trials," a relatively new concept in translational research, could soon dramatically change the way the pathology—and the paradigm of treatment—is viewed for patients with renal cell carcinoma (RCC).[1,2] The standard mouse model, important in the development and refinement of targeted therapies, is essentially being reinvented by co-clinical trials that significantly change the way animal models can mimic the clinical behavior of kidney tumors following a patient's surgery.

A co-clinical trial is a mouse study designed to mirror an ongoing clinical trial in patients whose tumors harbor the same driver mutations.[1,2]Animal models need to mimic clinical behavior as closely as possible to achieve meaningful insight into underlying molecular mechanisms.[3] Well-characterized models that mimic RCC and other cancers are required for a variety of reasons because they:

- Test the efficacy of novel drugs and their combinations.
- Study the mechanism of action of these drugs, thus elucidating the mechanism of resistance to such therapies.
- Seek to compare and extrapolate the response to therapy in mice to that of humans.
- Evaluate and validate novel biomarkers for prognosis and prediction of response to therapy.

RCC tumor models available for preclinical testing—such as commercially available high-passage cell lines maintained in culture—have been available for years but they have many limitations and there is an unmet need for a better tumor xenograft model of RCC that can be applied to the evaluation of a drug. The commercially available cell lines have been useful but their value is diminished by new mutations acquired during adaptation to growth in culture and subsequent expansion.[4,5] The tumors formed by cell lines in mice also tend to be poorly differentiated and likely dissimilar from the tumor from which the cell line was originally derived.[6,7] This is probably why they have limited use in predicting drug responsiveness in patients.[8]

Now there are promising signs that this need for a refined tumor xenograft model may be met. One of the key issues is whether such a model can be used in a "real time" setting. Our recent report on the development and characterization of a panel of surgical mouse models of RCC derived from patients with distinct RCC histologies is encouraging. The data emerging from this study reflect a similar direction taken by other investigators who have also developed xenograft models in other cancers, including colorectal, acute promyelocytic leukemia, and lung.

From the perspective of kidney cancer management, the latest findings are exciting for several reasons. The four xenograft models developed represent distinct RCC histologic subtypes using primary renal tumors obtained directly from patients at the time of radical nephrectomy; and the xenograft models grow after both subcutaneous and orthotopic implantation.[3] When characterizing these tumors, we found that these mouse xenograft models:

(1) Are stable during serial passages in mice.
(2) Faithfully capture the original human tumor genotype and phenotype.

Keywords: renal cell carcinoma, mouse model, xenograft tumor model, co-clinical trials.

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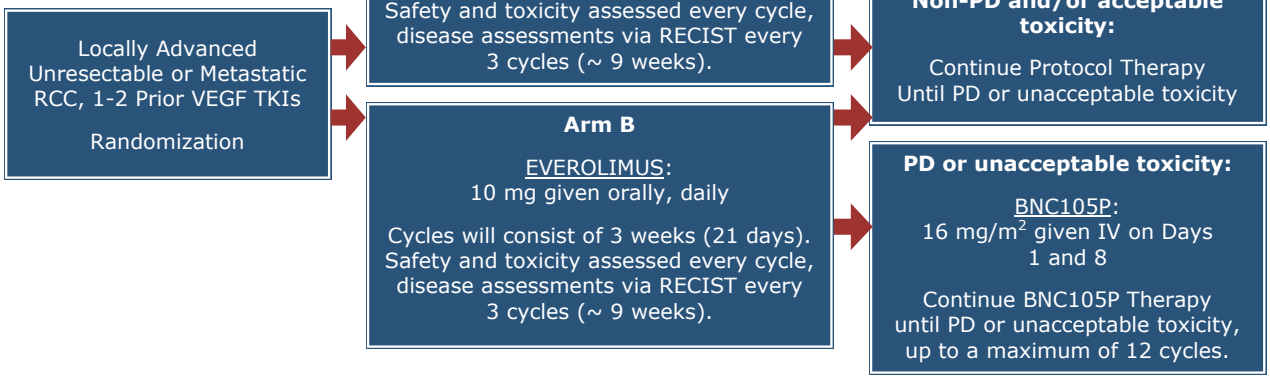
E-mail address: cgwood@mdanderson.org

Clinical Trial in Renal Cell Carcinoma

Now Open for Enrollment

A Phase II Study of BNC105P in Combination with Everolimus or Following Everolimus For Progressive Metastatic Clear Cell Renal Cell Carcinoma Following Prior Tyrosine Kinase Inhibitors

Study Design



Study Rationale

- BNC105P, a novel vascular disrupting agent, is an inhibitor of tubulin polymerization
- In vivo exposure to BNC105P leads to selective damage of tumor vasculature in both primary and metastatic lesions, causing disruption of blood flow to tumors, hypoxia and associated tumor necrosis
- BNC105P also has a direct anti-proliferative action on cancer cells
- Up regulation of the mTOR pathway has been identified as a cellular response to hypoxic stress
- The combined use of BNC105P with an agent active against mTOR may improve clinical outcome in patients with progressive mRCC who are refractory to VEGFR-directed TKIs

Objectives

Primary Objective

- Improvement in 6-month PFS with the addition of BNC105P to everolimus

Secondary Objectives

- To determine response rate with combination therapy compared to everolimus alone
- To determine PFS with BNC105P alone in patients progressing on everolimus
- To determine OS, up to a maximum of 5 years
- To evaluate the adverse events of the combination

Exploratory Objective

- To determine the correlation of PFS with biomarkers

Patient Population

- Histological or cytological proof of component (any percent) of clear cell RCC. NOTE: No component of collecting duct or medullary histology is allowed. Up to 30% sarcomatoid histology will be permitted
- Metastatic or locally advanced unresectable RCC. NOTE: Prior nephrectomy is not mandatory
- Progressive disease after 1-2 prior VEGF-directed tyrosine kinase inhibitors (TKIs). NOTE: Patients who did not tolerate a VEGF-directed TKI may also be considered (Sponsor is to be consulted)
- Measurable disease according to RECIST and obtained by imaging within 30 days prior to registration
- No active brain metastases. Patients with neurological symptoms must undergo a head CT scan or brain MRI to exclude brain metastasis within 30 days prior to registration
- No prior treatment with temsirolimus or everolimus

For More Information

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hoosier oncology group

(3) Mimic the clinical scenario when treated with targeted therapy by showing initial response to therapy but then demonstrate eventual resistance.

Although the results from co-clinical trials are generating excitement, they are still at the investigational stage and are not near the point where they can be applied clinically in a wide range of actual treatment situations. Nevertheless, the initial results with this approach highlight several reasons why RCC may be especially suited for the development of such xenograft models. For example, RCC tumors are typically large, offering access to abundant tumor material. Since RCC patients seldom undergo chemotherapy prior to surgery, the molecular genetics and behavior of the tumor are unlikely to be affected by earlier treatment with DNA altering agents.[8] There are other advantages apparent in RCC: the tumors implanted in mice preserve the histology and karyotype of patient tumors. Additionally, the site for orthotopic implantation of RCC—under the kidney capsule—is a good site for tumor growth. Since molecularly targeted therapies are typically used to treat RCC, such a tumor xenograft model allows for testing of this emerging class of drugs. Sivanand and colleagues implanted tumor samples from 94 patients in kidneys of mice to develop orthotopic mouse models of RCC.[8] Xenografts formed in 35 of these mice and 16 stable lines were developed. The authors reported that samples from metastatic sites engrafted at higher frequency than those from primary tumors, and stable engraftment of primary tumors in mice correlated with decreased patient survival. The tumor xenografts retained not only the morphology but the histology, gene expression, DNA copy number alterations, and more than 90% of the protein-coding gene mutations of the corresponding tumors. One of the interesting findings from this study was that RCC tumor xenograft growth was inhibited by sunitinib and sirolimus but not by erlotinib. In addition, dovitinib-an inhibitor of fibroblast growth factor receptor and vascular endothelial growth factor receptor-showed greater anti-tumor activity than sunitinib and sirolimus.[8]

How could this approach be utilized even though there is not as yet a certified clinical basis for its application? Theoretically, a tumor removed at the time of surgery could be brought to the laboratory and processed, grown in culture and transformed into a xenograft as well. After it is established within the mouse as part of a co-clinical trial, its susceptibility could be tested against a variety of agents to determine which modality would be most effective and what may constitute the best choice for first and second line therapy.

As researchers pursue additional models of cancer, they are also alluding to some of the shortcomings of earlier attempts to characterize the heterogeneous nature of RCC. Despite their invaluable significance for studying the genetic mechanisms at the basis of RCC development, these models represent types of kidney tumors (chromophobe RCC and oncocytoma) that account for only a limited number of cases in humans, according to Grisanzio et al.[9] In a study similar to that of Sivanand et al,[8] these authors transplanted intact human tumor tissue fragments orthotopically in immunodeficient mice. Their xenografts were validated by comparing the morphological, phenotypic, and genetic characteristics of the kidney tumor tissues before and after implantation. After 20 tumors were transplanted into mice, tumors grew in 19 of the 20 mice. Grisanzio et al found that the histopathological and immunophenotypic features of the xenografts and those of the original tumors largely overlapped in all cases. Notably, an evaluation of genetic alterations in a subset of 10 cases demonstrated that the grafts largely retained the genetic features of the pre-implantation RCC tissues. Primary tumors and corresponding grafts had identical VHL mutation. In addition, an identical pattern of DNA copy alterations was documented in 6 of 10 cases.

Although extensive validation studies are still required before orthotopic RCC models are widely used in the preclinical setting, this study demonstrated high levels of histological, phenotypic, and genetic concordance between the xenografts and the corresponding primary tumors. The authors readily acknowledge several shortcomings that the field faces—issues that need to be addressed in further genomic analyses of larger series of pre- and post-implantation tumor tissues as well as functional studies. For example, there were some genetic alterations detected in the xenografts but not in the corresponding primary tumors that could play a functional role in tumor growth and progression in RCC. They offer some explanations for this discrepancy. For example, the heterogeneity of genetic alterations in different regions of the primary tumors may help explain abnormalities present in the original tumor but not in the matched graft, according to their review of earlier literature.

As investigators seek to develop stable xenograft models that overcome these issues they need to address whether the models can provide a better understanding of metastases. Major efforts have been made to study human renal cancer growth and progression in vivo, especially metastasis development. Two of the xenograft tumors in the study by Grisanzio et al invaded contiguous organs, and one of two RCC cases known to have caused metastases in patients also produced multiple lung metastases in the murine hosts. This was an encouraging sign that at least a subset of the RCC xenograft models had the potential to reproduce metastatic patterns of human cancer in vivo and could offer clues for examining genetic and epigenetic events critical to RCC cell dissemination. Perhaps further studies of similar subpopulations could indeed be useful in developing novel therapeutic treatments.

All of these RCC models focus on clear-cell histology, the most prevalent subtype of RCC. Thus, a clear unmet need exists for developing new models for other RCC subtypes, such as papillary RCC. There is one mouse

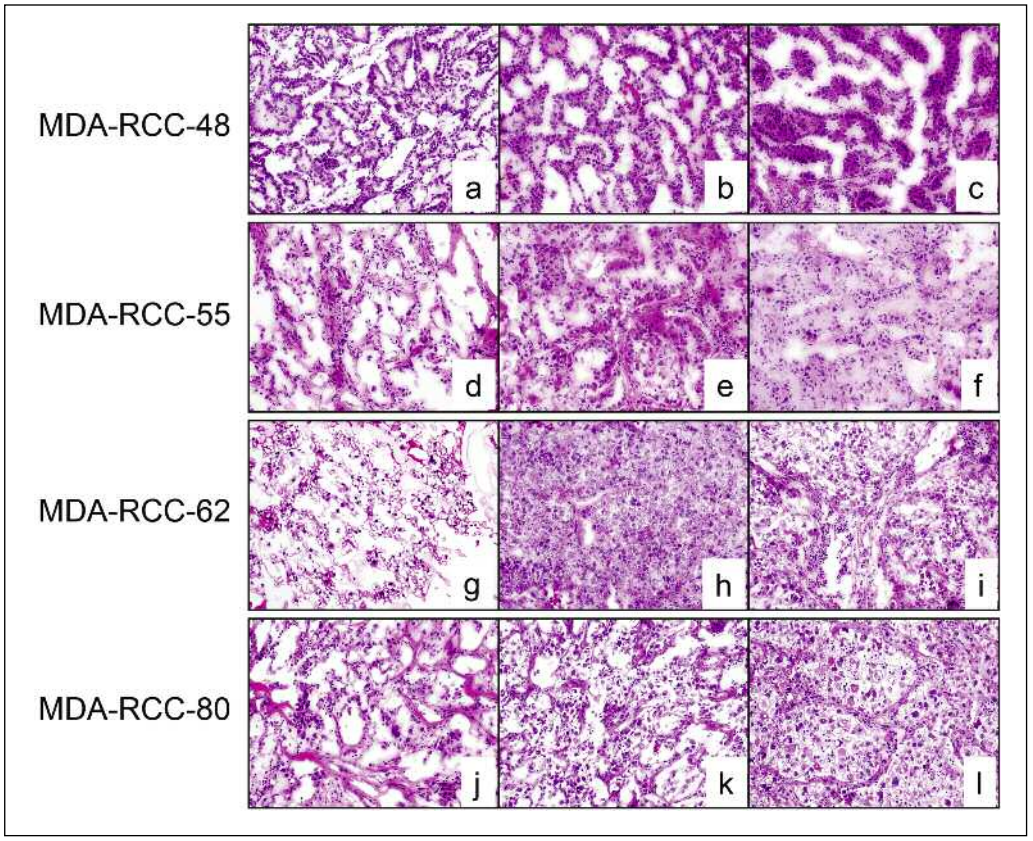


Figure 1. Hematocylin and eosin sections of four patient-derived renal cell carcinoma tumors comparing the original patient tumor and the three subsequent passages in nude mice: (a,b,c) MDA-RCC-48-P, F3, and F7, respectively; (d,e,f) MDA-RCC-55-P, F2, and F6, respectively; (g,h,i,) MDA-RCC-62-P, F2, and F5, respectively; (j,k,l) MDA-RCC-80-P, F2, and F15, respectively. (Reprinted by permission of *European Urology*. Source: Karam JA, Zhang X-Y, Tamboli P, et al. Development and characterization of clinically relevant tumor models from patients with renal cell carcinoma. *Eur Urol*. 2011;59:619-628).

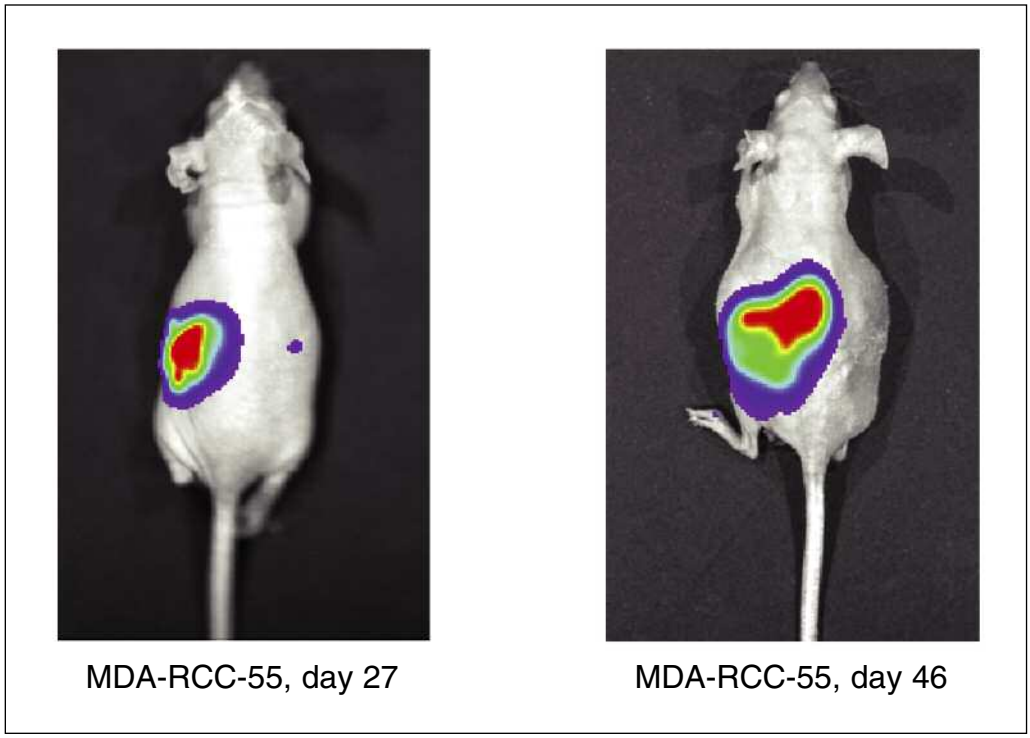
model of papillary RCC[10] but its characterization and stability has not been well studied. This is why findings from our recent study are important: we developed four mouse xenograft models of RCC with clear-cell and papillary histologies, with stable histologic and molecular characteristics. We also explored whether treatment with several targeted agents could elicit a response and to what extent the xenograft model could mimic the later stage resistance so often observed in humans.

We described four distinct tumor types derived from four different patients, removing tumor fragments only from patients with advanced stages of RCC to improve the chances of implantation and propagation.[3] Tissues from patients of different ages, genders and ethnicities were used to establish the xenograft models and were derived from viable areas in the primary renal tumor. After establishing model stability, mice were treated daily (**Figure 1**) with sunitinib or everolimus and followed for re-sponse to treatment.

Tumors in mice accurately represented their respective original patient tumors, as STR fingerprints were matching, histology was comparable, and SNP profiles and VHL mutation status were conserved with multiple passages. Results from bioluminescence imaging showed feasibility of this imaging approach in the orthotopic xenograft setting. A key finding was the response to treatment: mice treated with sunitinib and everolimus showed an initial response, followed by a later stage of resistance to these agents. This mimics the clinical observations in patients with RCC (**Figure 2a-b**, page 74).

As noted with respect to other xenograft findings, the results from this study are highly investigational but the implications for potential application are exciting and far reaching despite the limitations also observed in this report. One of the limitations concerns heterogeneity, given the recent findings of Gerlinger et al.[11] Future studies need to address whether the portion of the tumor derived from a patient and implanted in the mouse model is indeed the most aggressive portion of the patient's tumor. Another concern involves the viability of the tumor once implanted in the mouse. Not every tumor derived from a patient during nephrectomy establishes itself in a mouse model; there is a 20% to 25% "dropout" rate and some tumors simply do not grow once implanted.

Nevertheless, there are some practical advantages to the approach taken in our study[3] that point toward potential value in clinical situations. One is the amount of time that elapses between implantation and establishment of the tumor in the mouse model. The process of establishing the tumor in mice generally requires 4 to 6 weeks, a period commensurate with the 4 to 6 weeks a patient requires to recover from a radical nephrectomy. Thus, by the time the xenograft is established a patient has approximately reached the stage where he or she is ready to begin treatment with a targeted agent. Perhaps, the xenograft model may not yield much insight into whether the patient is a candidate for a specific first-line therapy but it could provide important information on appropriate second or third line therapy. The xenograft model could be treated in tandem with the patient from which is was derived in the front line setting, to validate the model as it should respond in similar fashion to the response seen clinically in the patient. After progression is seen in the xenograft model, different second line agents could be tested, to provide insight into the most



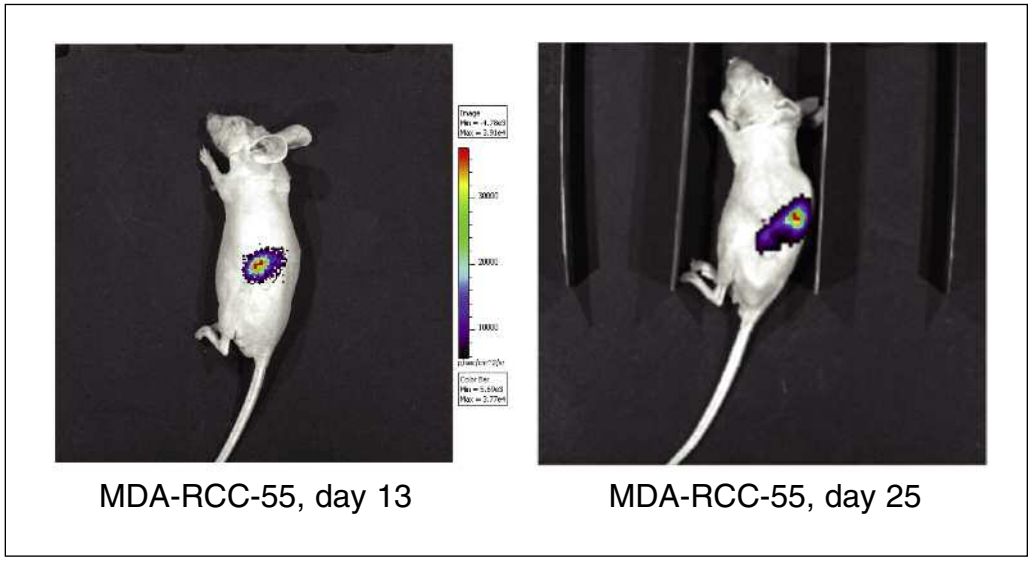
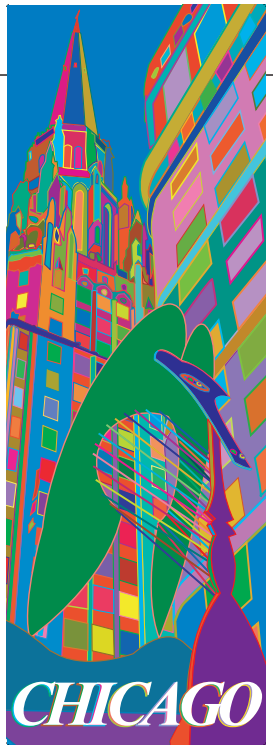


Figure 2a, 2b. In vivo bioluminescence imaging in two renal cell carcinoma tumor types at different days: (a) MDA-RCC-55; (b) MDA-RCC-M80. (Reprinted by permission of *European Urology*. Source: Karam JA, Zhang X-Y, Tamboli P, et al. Development and characterization of clinically relevant tumor models from patients with renal cell carcinoma. *Eur Urol*. 2011;59:619-628).

appropriate salvage therapy for the patient at the time of progression. Still, another potential benefit suggested in our study is the possibility of developing an entire panel or "library" of surgical mouse models of RCC derived from patients with distinct RCC histologies. Although further study is needed on additional xenografts and results are yet to be published, we have developed xenografts for a spectrum of RCC, including papillary type 1, papillary type 2, Xp11 translocation, and renal medullary carcinoma in addition to the clear cell variety. Further study needs to address whether xenografts in these and other RCC types can form the basis for stable models that will retain features of the primary tumors from which they were derived and whether treatment strategies can be evaluated as well.

Perhaps studies in other cancers will elucidate the extent to which mouse models will be highly useful in discovering predictive biomarkers and gaining insights into clinical outcomes and drug resistance. It is unclear whether the findings from these other studies, including models involving lung and pancreatic adenocarcinoma, colorectal cancer, and other advanced cancers can be extrapolated to RCC. But they suggest how research in RCC might be guided and how the gap between preclinical data and trial outcomes could be narrowed. For example, a study by Bertotti et al[12] showed how a suite of patient-derived xenografts from metastatic colorectal carcinomas reliably mimicked disease response in humans. It prospectively recapitulated biomarker-based case stratification and identified HER2 as a predictor of resistance to anti-epidermal growth factor receptor antibodies and of response to combination therapies against HER2 and epidermal growth factor receptor. Their study was based on xenograft co-horts from 85 patient-derived colorectal cancer samples. Studies such as the one by Bertotti et al[12] hopefully will provide additional lines of evidence that the preclinical xenograft platform can provide an improved framework for determining potential treatment efficacy.

From studies of xenograft models in other cancers, data are emerging that such personalized tumor xenograft models could serve as a powerful investigational platform for therapeutic decision-making and to efficiently guide cancer treatment in the clinic. This view was espoused by Hidalgo et al[13] whose study reported on tumors excised from 14 patients with treatment-refractory advanced cancers that were then implanted in immunodeficient mice and treated with 63



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drugs in 232 different treatment combinations. An effective treatment in the xenograft model was identified in 12 patients. One patient died before receiving treatment and the remaining 11 patients received 17 prospectively guided treatments; 15 of these treatments resulted in durable partial remissions. The study authors concluded that there was a good correlation between the drug activity in the mouse model and clinical outcome. The objective response rate was 88% for treatments deemed effective by the model and tested in the patients. This efficacy contrasts with the expected response rate with Phase 1 agents, the only available option for some of these patients, of 10%.

One area that will provide fertile territory for additional exploration involves the poorly understood biology underlying the heterogeneity of tumors and the impact of co-existing genetic mutations. Chen et al[14] used genetically engineered mouse models to conduct a co-clinical trial that mirrored an ongoing human clinical trials in patients with KRAS-mutant lung cancers. They observed that adding selumetinib to a standard chemotherapy resulted in marked benefit for mice with lung cancer caused by K ras and K ras and p53 mutations but mice with K ras and Lkb1 mutations had primary resistance to this regimen. PET and CT imaging were able to define biomarkers in mice and patients that could explain the differential efficacy of these treatments in the different genotypes. The take-home message from this study is that beyond assessing genetic modulators, co-clinical studies allow for validation of biomarker strategies and discovery of mechanisms of resistance that could be of benefit to future clinical trials. The FDG-PET imaging could be a useful biomarker strategy for identifying a responder population and predicting long-term outcome.

Despite their optimism, authors of this and other studies continue to highlight the investigational nature of these approaches and the limitations that still need to be resolved. Fresh tumor material and intense resources are needed to generate the xenografts. Even in the best conditions, 25% to 30% of implants fail, and those that engraft may require up to 6 to 8 months of additional propagation in some advanced cancers to be useful for treatment[11], although the lag time appears to be significantly less for the RCC xenografts.

Even with these limitations, however, the future is bright for co-clinical trials and efforts are proceeding at several institutions to integrate the knowledge gained from numerous studies as part of the emerging "Co-Clinical Trial" Project.[2] A new paradigm may ultimately assert itself as part of a vision for the integration of all the components from various programs involved in co-clinical trials. Nardella et al[2] envision the development of central cancer mouse hospitals where large-scale mouse trials can be conducted and evaluated by experts in close consultation with clinicians and pharmaceutical companies. These facilities would include comprehensive, high throughput biomarker analysis of a host physiologic response to treatment to support co-clinical human-mouse trials. The groundwork for this futuristic vision is already beginning at a number of leading cancer treatment centers in the U.S., including ours, as part of providing the proof of concept that co-clinical trials could provide a new paradigm for the treatment of patients with cancer.

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Sarcomatoid RCC: The Challenge of Understanding and Developing Treatment Strategies for An Aggressive Variant of Kidney Cancer

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One kidney cancer type remains a therapeutic dilemma—the sarcomatoid variant of renal cell carcinoma (RCC). While the nomenclature has changed from a distinct histologic subtype to a feature, the aggressive nature and limited treatment options remain a formidable treatment challenge. The presence of sarcomatoid features is not only an independent predictor of poor survival but may be one of the most influential prognostic variables for patient outcome. Nevertheless, the enigma of this cancer is beginning to be clarified as well as an improved understanding of pathological features associated with response to therapy and prognosis. However for the most part when metastatic, this disease still remains difficult to treat despite efforts to combine immunotherapy, cytotoxic agents and targeted therapies.

Introduction

One of the most daunting challenges in kidney cancer management is the treatment of sarcomatoid renal cell carcinoma (sRCC). Treatment of this histologic subtype has been called a therapeutic conundrum by some authors despite the availability of a growing spectrum of targeted agents and advances in systemic therapies.[1] sRCC is an elusive entity and for half a century misconceptions and misperceptions about it are prevalent, largely because of a poor understanding of its biology. When a tumor has been as inadequately characterized as sRCC, an unmet need exists for more information on its pathological characteristics, histologic features, and the implications for treatment. Without an improved understanding of sRCC, clinicians face formidable challenges to reverse the progression of this highly lethal form of kidney cancer. Although it accounts for only about 5% of RCCs, the aggressive nature and advanced stage of presentation makes this entity fairly common to practitioners who manage metastatic disease.[2,3] Highlighting the need for more information is the fact that the sarcomatoid variant of RCC can account for approximately one in six cases of advanced kidney cancer.[1]

However, on the bright side, there is hope that the clinical picture may soon improve. While the prognosis currently remains uniformly poor the future is encouraging due to improved understanding of possible mechanisms of sarcomatoid transformation, new classes of available agents, an improved understanding of the predictive features of therapeutic response, and a renewed interest in trials aimed at this biologic entity (including combination therapy with immunotherapy, cytotoxic therapy, and targeted agents).[1]

History

The historical record on sRCC is rife with numerous misconceptions about this tumor. Initially pathologists looked at renal tumors with sarcoma-like appearances and characterized them as renal sarcomas.[2] The characterization has evolved over the years as pathologists began to recognize classic RCC features in many of these tumors and distinguished them as being epithelial tumors with sarcomatoid elements. The nomenclature and how to characterize it was ambiguous in the literature for several years and it was categorized as a separate histologic type due to its highly aggressive nature.[4] But classification of these tumors as a separate histologic type lost credibility in the recent World Health Organization classification system because sarcomatoid features were being observed in association with every histologic type of renal tumor.[3]

The controversy is still far from settled but the reasons underlying the varying classification scheme are at least more clearly defined. In the 1990s, the classification schemes eschewed most of the previous schemes and considered sRCC to be a feature related to extensive chromosomal rearrangements.[5,6] The popular conception during this time was that these so-called rearrangements led to identical spindle-cell morphology regardless of the primary epithelial histology. In 2001,

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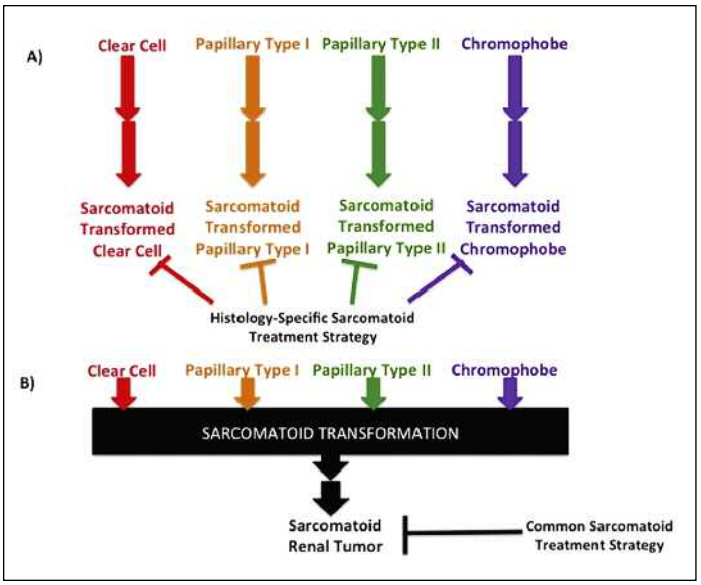

Figure 1. Potential biologic implication of sarcomatoid transformation on the development of specific therapy; a) histology-specific strategy, and b) common sarcomatoid treatment strategy.

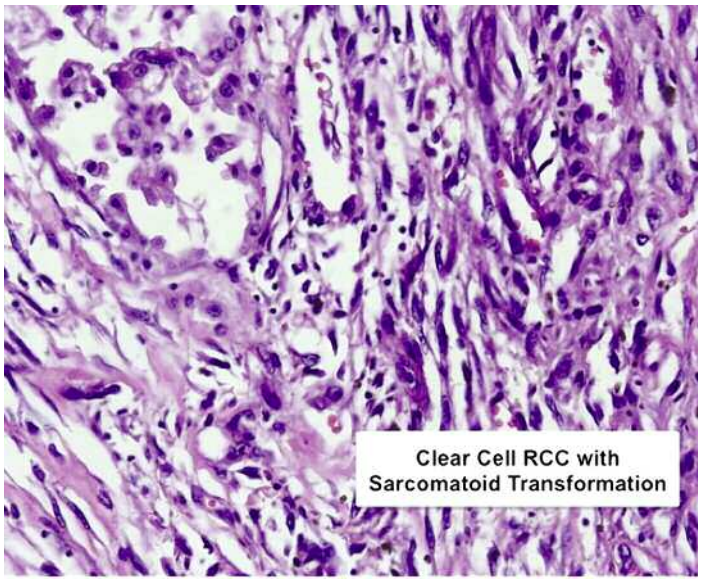

Figure 2. H&E of clear cell RCC with sarcomatoid transformed demonstrating classic elongated, spindle shaped cells (20X magnification). (Image provided by Jonathan Said, MD, UCLA School of Medicine, Los Angeles, California).

Delahunt et al[7] introduced a new view that also gained support. They suggested that sRCC was "the final common de-differentiation pathway" for renal tumors. Even today the debate over its characteristics is unsettled. Although leading pathology groups have reclassified sRCC, many urologic and medical oncologists recognize sRCC to be its own entity because of its poor prognosis and relative resistance to multiple forms of systemic therapy.[2,3] A major question in the future will be if there truly is a common pathway towards sarcomatoid differentiation, should this dictate a common treatment strategy or should the focus be on the primary histology (**Figure 1**).

Biology

Sarcomatoid RCC displays elongated, spindle-shaped cells, high cellularity and cellular atypia (**Figure 2**). A review of reports exploring its histologic characteristics include the following:

- Regions of sarcomatoid transformation which have no demonstratable epithelial components should not be considered sarcomatoid.[3]
- Wavy or rhabdoid regions that completely maintain epithelial features also should not be considered sarcomatoid.
- Common uniform histologic patterns can resemble fibrosarcoma or malignant fibrous histocytoma, however these patterns can widely vary.
- The majority of tumors have a variable amount of recognizable carcinoma elements and additional tumor blocks may be needed by the pathologist for assessment.
- The epithelial component may originate from any of the well-described RCC histologic subtypes. Clear cell RCC is the most frequently observed subtype accounting for ~65% of sRCCs.[4,8]

While the development of sarcomatoid transformation is poorly understood, recent research has implicated several pathways that may be involved in this process. Jakobsen[9] identified a lack of both β-microglobulin expression and major histocompatibility complex (MHC) class 1 expression in a cell line derived from a patient with sRCC. They suggest that a lack of this complex precludes antigen expression and allows for immune invasion. An early report by Kuriowa et al[10] also examined immunohistochemical analysis in sRCC specimens and found that E-cadherin expression in the sarcomatoid component was consistently lower than in the non-sarcomatoid component. Since E-cadherin plays an integral role in intracellular adhesion and is one of the hallmarks of epithelial-mesenchymal transformation (EMT), this may explain the greater malignant potential of sarcomatoid RCC.[5] Recently Conant and colleagues confirmed that EMT may be the primary process responsible for sarcomatoid transformation. Immunohistochemistry (IHC) studies between matched pairs of sarcomatoid and clear cell areas demonstrated classic EMT features such as E to N-Cad-herin switching as well as SNAIL and ß-catenin alterations.[6]

Diagnosis

Primary renal sarcomas are extremely rare in adults, accounting for <1% of renal malignancies. When found, however, nearly 50% are leiomyosarcomas; these leiomyosarcomas contain smooth muscle components and are rarely found in sRCCs.[11] Primary renal sarcomas should not contain any classic areas of RCC, a sign that the tumor is of epithelial origin. To confirm the diagnosis, electron microscopy and immunohistochemistry (IHC) may be helpful, the microscopy to visualize epi-

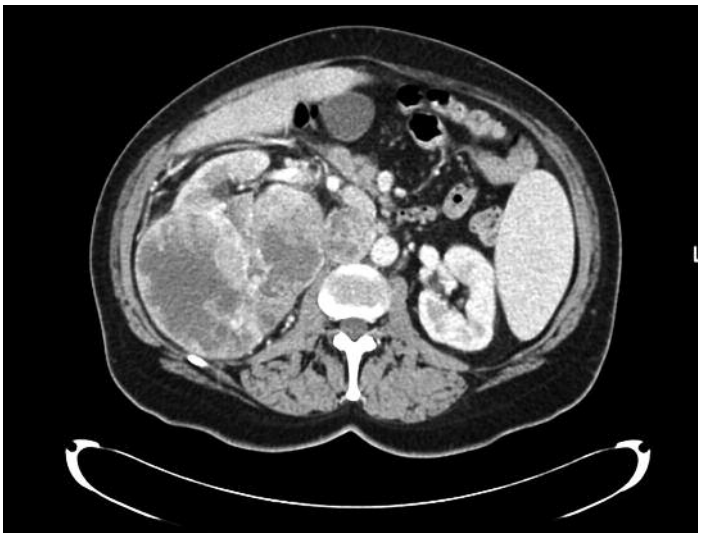

Figure 3. CT scan demonstrating a 12 cm, right renal mass with bulky regional lymphadenopathy. On final pathology this was found to be a T3N1M0 clear cell RCC with sarcomatoid transformation.

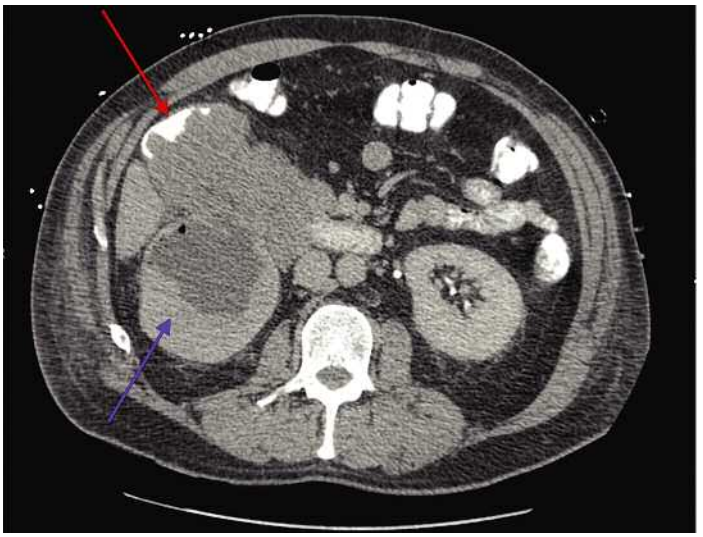

Figure 4. CT scan demonstrating a 10 cm, right renal mass (blue arrow) invading into the duodenum (red arrow). This patient had a predominantly sarcomatoid transformed clear cell tumor. After cytoreductive nephrectomy, rapid liver progression and carcinomatosis ensued and the patient was passed away prior to the initiation of systemic therapy. (Image provided by David Finley, MD, Kaiser Sunset, Los Angeles, California).

thelial components (such as desmosomes) and IHC for epithelial markers such as cytokeratins that distinguish sRCC from sarcoma.[7]

Clinical Presentation

Numerous studies highlight the aggressive nature of sRCC. The presentation is closely associated with the stage at diagnosis. Most series suggest that:

- Sarcomatoid tumors are usually extremely large (with a mean tumor size of 9-10 cm) and nodal disease is common (**Figure 3**)
- Up to 25% of sRCC present with T4 disease (**Figure 4**)
- Approximately 50-70% are metastatic at presentation.[4,8]
- Approximately 90% are symptomatic at presentation.[12,13,14-16]
- Locations of metastases are similar to that of other renal tumors: the most common are lungs, bone, nodes, liver, and brain. [4,1]

Preoperative identification

If sarcomatoid histology could be identified preoperatively, it is feasible the surgical approach may change. If these features are evident in distant lesions, the primary tumor may also have such features, but therein lies a pitfall: one report evaluating distant sites of metastases from sRCC found that >30% of distant lesions contained the non-sarcomatoid elements. Thus, the absence of sarcomatoid features at metastatectomy or biopsy has a low specificity in predicting sarcomatoid histology in the primary tumor.[17]

Can renal biopsy readily identify sarcomatoid histology? This approach is also limited because:

1) The amount of tissue obtained from a 16- to 18-gauge core biopsy may be non-diagnostic for large masses.
2) Tumor heterogeneity of sRCC can lead to sampling error because over half of these tumors contain <50% sarcomatoid features.
3) The histologic architecture after fixation and processing may not be sufficiently maintained to reliably differentiate sRCC from high-grade carcinoma or sarcoma.

There are several reasons why the development of a preoperative, predictive marker of sarcomatoid histology is needed for both metastatic and localized renal tumors.[1] The standard of care in the immunotherapy era has been cytoreductive nephrectomy for select patients with good performance status based on a perceived survival benefit. While the benefit of debulking is less clear in the targeted therapy era, there is little argument that those patients with rapidly progressive extra-renal disease do not benefit from surgery (**Figure 4**). Because many patients with sRCC have rapidly progressive disease many of these patients have not been able to proceed to systemic therapy.[1,12] Surgery alone in the setting of metastatic RCC is not believed to greatly prolong survival, so its likely that these patients did not derive clinical benefit from surgery.[13] Whether patients would have improvement in survival if identified and received systemic therapy first is unknown, however patients may have been spared unnecessary morbidity of surgery. Recent studies involving patients with presurgical therapy have demonstrated that perhaps upfront systemic therapy could select out those who may derive less benefit from cytoreduction.[14]

For localized renal masses, a partial nephrectomy has been considered by many to be the standard of care for the small renal mass. Some proponents of partial neph-

rectomy have also pushed this approach to larger tumors. The margin of resection has diminished over time with some centers advocating a mini-margin or performing enucleation. For sRCC, if identified, one may consider using a more aggressive approach by performing a radical nephrectomy when feasible. Ad-ditionally due to the advanced nature and propensity for nodal spread, a lymph node dissection should be considered even with negative imaging.[15] The large size and infiltrative nature of these tumors sRCC may make partial nephrectomy more challenging. Anecdotally, we have observed several aggressive, local recurrences when nephron-sparing has been performed (**Figure 5**). In retrospect, perhaps if we had known more about the aggressive nature of the primary, our surgical approach likely would have differed.

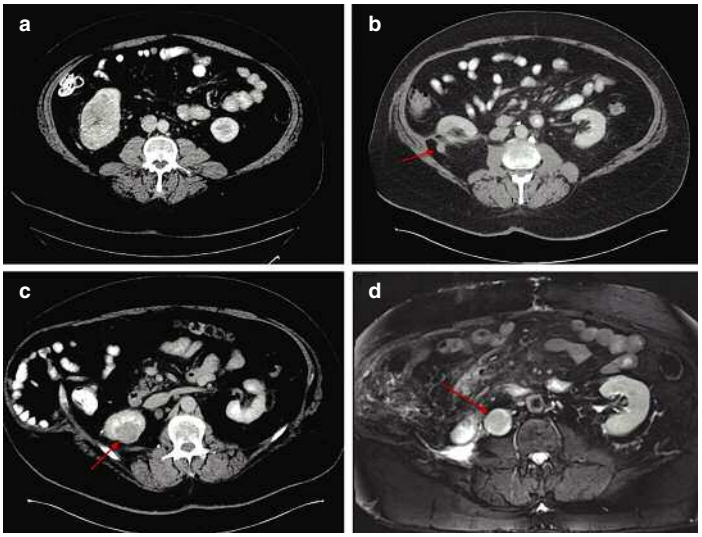

Figure 5a-d. a) A large (7cm) exophytic, lower pole renal mass treated with partial nephrectomy. Final pathology was a T2 clear cell tumor with approximately 50% sarcomatoid features. b) 15 months later, the patient presented with a renal fossa recurrence (red arrow) which was resected. c) 14 months later the patient developed a 3 cm lower pole mass (red arrow). A radical nephrectomy and extensive node dissection was performed demonstrating similar pathology as the initial surgery. d) 6 months later, the patient developed a 3 cm renal fossa recurrence (red arrow).

Prognosis: Pathological Features That Predict Outcome

There is little doubt in the literature about the poor prognosis in sRCC: it tends to have the worst prognosis of all renal tumors. Extended survival after diagnosis is rare with the majority of cases showing a median survival time of only 4-9 months for stage IV disease.[3] For pa-tients with stage III disease, select patients can be cured with an aggressive surgical approach. However, it has been our approach to refer these patients for adjuvant trials due to the high likelihood of recurrence. Only stage I and II sRCCs generally are associated with longer survival. It is clear that that the presence of sarcomatoid features are not only an independent predictor of poor survival but may be one of the most influential prognostic variables.[18]

Despite this scenario, any effort to improve prognostication begins with an understanding of the influence of pathologic features such as histological subtype, type of sarcomatoid morphology, the percentage necrosis, and the percentage of sarcomatoid features, and the presence of miscrovascular invasion.[8] This was the focus of our study on the impact of pathological tumor characteristics. Some of these identified characteristics may be important to the current and future trials specifically targeted patients with sRCC, some of which have stratified patients based on histological features. These features include clear-cell vs non-clear cell histology and by the percentage of sarcomatoid features (PSF) in the primary tumor. Stratification could help assess therapeutic response if the histology and the PSF influences the disease biology. A current study[8] explored the role of pathological characteristics in determining biology and outcome. Our consecutive series of 104 patients with sRCC treated with nephrectomy at a single institution (UCLA) found that the median size of tumors was 9.5 cm, 65% of patients had areas of clear cell histology, and 69.2% had metastatic disease at presentation. The study confirmed the extremely poor outcome in sRCC, with median survival of <6 months for all patients. While several series have demonstrated longer survival for patients with sRCC, this could be related to a bias of healthier patients being referred to a tertiary care center for systemic therapy. Comparing our cohort to the Surveillance Epidemiology and End Result (SEER) program, survival and tumor characteristics were nearly identical.[16]

Percentage sarcomatoid features. Our report indicated that while PSF has no association with tumor size, stage, necrosis, microvascular invasion or the presence of lymph nodes or metastases, there was a strong association with survival. The findings also confirmed results from prior series in which increased sarcomatoid change was associated with poor survival.[12,19] Either as a continuous variable or by quartile, increased PSF appears to influence prognosis. Among the patients with non-metastatic sRCC, PSF was the only significant predictor of survival. While several series have selected specific cut-points of PSF (such as 50%), we have been unable to identify a specific evidence-based, cut-point for PSF influencing outcome.

Microvascular invasion. Previous reports demonstrate a worse survival after nephrectomy in sRCC among patients with MVI, a finding that held true in the study by Shuch et al. There was MVI in 50% of cases and this feature was an independent predictor of poor outcome. MVI should be increasingly considered as a useful component in prognostication, yet many pathologists do not mention the presence or absence of this feature in pathology report. Another one of our series observed that less than half of nephrectomy pathology reports mention this variable.[20]

Histological pattern of sarcomatoid change. Although many studies of non-sacromatoid renal tumors

have found an association between clear-cell histology and advanced stage and tumor size, thereby possibly influencing prognosis, this may be less relevant to sRCC.[8] Although reporting the primary histology may have a biologic significance to treating clinicians and trial design, it does not appear to influence prognosis. No associations between histology and clinicopathological variables emerged. The grade of the carcinoma element associated with sRCC is also not considered an influential factor. While several recognizable patterns of sarcomatoid change exist, this also many not influence prognosis.

Overall, the caveat for clinicians is that patients with localized disease, especially among those with high PSF, extremely close follow-up is essential and this group should also be considered for adjuvant trials. There is no shortage of nomograms and algorithms for post-nephrectomy RCC, but none specifically targeted for sRCC. It is relatively easy to figure out why this has not been the case. First, some of the commonly used models were specifically designed for patients with clear-cell RCC and have not even been evaluated in non-clear cell RCC. Then there is the issue of risk—sRCC consists of such a high-risk group it is highly uncertain how models primarily developed for low- and intermediate-risk patients would perform in the setting of sRCC. Another factor arguing against applicability in sRCC is that other models of high-risk patients were developed in the context of metastatic disease undergoing systemic therapy. These models cannot be used for locally advanced/regional tumors.[21,22] From our large cohort we demonstrated that such a nomogram is feasible. Using six covariates including tumor size, necrosis, MVI, PSF, performance status, and the presence of metastasis the model was adequate with AUC values ranging from 0.67 to 0.78. Prior to a model like this be accepted, it would require extensive calibration and external validation.

Defining Outcomes with Systemic Therapy: The Latest Analysis

Scant data are available to assess the role of various therapies in sRCC. A recent retrospective analysis,[1] however, offers insights as it defined outcomes associated with systemic therapy, including immunotherapy, cytotoxic therapy, and targeted agents, with attention to novel prognostic schema.

The question of whether immunotherapy may be of benefit in sRCC has been addressed but the data compiled from a UCLA study of high-dose interleukin-2 (IL-2) also represent a cautionary tale, despite some favorable results. Cangiano et al[23] assessed a cohort of 31 patients with sRCC who had undergone nephrectomy. In the cohort 28 patients had metastatic disease and 9 patients received high-dose IL-2. Several responses were seen including two complete responders. A later internal review of these cases demonstrated that most of the IL-2 responses with in tumors with predominantly clear cell RCC with <30% PSF. Improved survival was seen in those receiving high-dose IL-2 but the sample size was too small to suggest anything definitive.

Chemotherapy has played a role in chemotherapy for many highly aggressive sarcomas. This has also been introduced into the treatment algorithm for patients with sRCC with mixed results: Doxorubicin and Ifosfamide have shown to be a highly ineffective regimen for this patient population. There is some some efficacy in patients with sRCC and those with rapidly progressive disease with a regimen combining Gemcitabine and Doxorubicin. However later experience with this regimen has mixed results.[17,18]

Targeted therapy has given new hope to patients with metastatic RCC, however in sRCC the results have been less encouraging. Golshayan et al[24] in a study of 43 patients treated with targeted therapy at the Cleveland Clinic. While patients with sRCC derived from clear cell tumors may demonstrate partial responses, overall, the response appeared worse than for routine clear cell tumors.[24] Staehler also demonstrated that sRCC could respond to sorafenib, however progression-free survival was far worse than that observed in other series.[17]

Pal and colleagues reviewed their experience with sRCC from an institutional database of 270 patients with metastatic RCC; 34 patients had documented sarcomatoid features. Within this cohort, 21 patients received systemic therapy; 2 received chemotherapy, 7 immunotherapy, and 12 received targeted agents as their first-line therapy. Median overall survival (OS) in the overall cohort was 18 months; patients with poor risk had a median OS of 4.7 months vs 20.1 months for patients with intermediate-risk disease. There was no significant difference in survival in patients with sarcomatoid predominant disease vs non-predominant disease, nor was there a difference among patients receiving targeted therapies vs non-targeted therapies. Given the lack of major differences in survival in this series between targeted therapies and immunotherapy, this study underscores the need for prospective evaluations directly comparing these treatment approaches. Until that happens, the conundrum about devising a treatment algorithm will remain precisely that—a therapeutic dilemma.

Pal et al[1] conclude that ultimately the cutting edge of treatment of sRCC will hinge on an improved understanding of the biology of the disease. There are some glimmers that headway is being made on this front. If an improved understanding of the biology of sRCC emerges, perhaps such insights can promote an effective treatment approach. Most of the data gathered so far on therapy are anecdotal reports suggesting the efficacy of a wide array of treatment options.[1] The "take-home message" is that metastatic sRCC remains a virtually untreatable disease. The field anxiously awaits the results of current phase 2 and phase 3 trials combining targeted agents, cytotoxic therapies and possibly immunotherapy as investigators seek to validate a clinical algorithm.

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EDITOR'S MEMO

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according to a recent report in *Cancer Discovery* (Nardella C, et al. The APL Paradigm and the "Co-Clinical Trial" Project. *Cancer Discovery*. 2011;1:108-116).

As fascinating as these projections are, we are not there yet. We need to focus first on moving the current models forward, and learn how primary tumor xenograft models of RCC with clear-cell and papillary histologies and stable histologic and molecular characteristics can help us identify mechanisms of action, molecular correlates of response, and resistance to novel targeted therapies.

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Highlights from the Kidney Cancer Association Meeting, Chicago, October 5-6, 2012

Selected Abstracts from the 11th International Kidney Cancer Symposium Meeting: Genomics, Biomarkers, Diagnosis, New Targeted Agents

The 11th International Kidney Cancer Symposium featured abstracts covering the latest trends in diagnosis, management and translational research, comprising one of the most comprehensive oncologic agendas of any scientific meeting this year. Summaries of selected abstracts are presented in this report. A complete publication of all abstracts appeared in the *BJU International* and is available online at: (http://onlinelibrary.wiley.com/doi/10.1111/bju.2012.110.issue-s2/ issuetoc).

Preexisting hypertension is associated with advanced tumor stage but improved cancer specific survival in clear cell renal cell carcinoma. Hakim AA, Fiegoli B, Zabor EC, et al.

Summary: The authors identified 2,147 patients with clear cell renal cell carcinoma (ccRCC) who underwent surgery from 1995 to2012. Higher body mass index (BMI) was associated with lower AJCC stage while hypertension and higher chronic kidney disease stage were associated with higher AJCC stage. Multivariate analysis showed that hypertension was paradoxically associated with improved cancer specific mortality and overall mortality. Analysis of hypertension by AJCC stage showed an association between hypertension and improved cancer specific survival in stages 3 and 4 but not for stages 1 and 2.

Conclusion: Hypertension is associated with advanced AJCC stage in ccRCC, but improved cancer specific survival in locally advanced and metastatic disease. This paradoxical finding suggests the possibility that preexisting hypertension might predict improved treatment response for advanced disease.

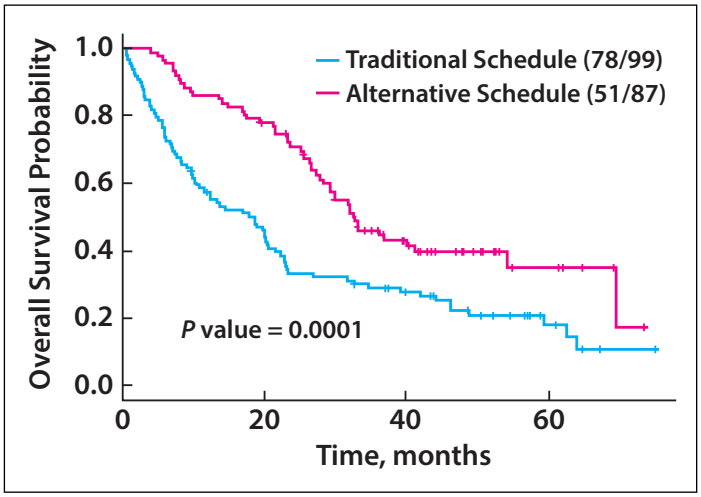
Tumor suppressor screens of 3p chromatin modulators link BAP1 mutations to poor clinical outcomes in clear cell renal cell carcinoma. Hakimi AA, Chen Y-B, Wren J, et al.

Summary: This study sequenced three of the most mutated chromatin modifiers (PBRM1, SETD2, BAP1) located on chromosome 3p in 190 patients who underwent primary resection at Memorial Sloan Kettering Cancer Center (MSKCC) to assess their frequency and association with clinical outcomes as a discovery set. Findings were then validated with data from the Cancer Genome Atlas (TCGA) ccRCC dataset (n=424. Both the MSKCC and the TCGA cohorts and the combined cohort showed strong associations with BAP1 mutations and worse cancer specific survival (P<0.001). When controlling for advanced tumor stage and grade, the study found that BAP1 mutations retained independent significance for worse cancer specific survival. None of the other genes was associated with adverse cancer specific or overall survival.

Conclusion: PBRM1 represents the second most common mutation event in ccRCC but does not impact clinical outcome, suggesting its role as an initiating event. BAP1 mutations are associated with worse cancer specific survival in ccRCC independent of tumor stage and grade. Further study of BAP1 in prognostic models and therapies directed toward this tumor suppressor in ccRCC are warranted.

Improved outcomes with sunitinib alternative schedule compared to traditional schedule: a single-center retrospective review. Atkinson B, Kalra S, Wang X, et al.

Summary: The recommended dose of sunitinib is 50 mg daily; 28 days (d) on/14 d off (traditional schedule, TS). An ideal treatment modification algorithm is unknown. Patients included those receiving sunitinib as first-line antiangiogenic therapy. A subset of patients were switched at first intolerable AE from TS to a 14 d/7 d, or further adjusted to 7 d/3 d, or other alternate



schedule (AS). The control group underwent standard dose reduction. Of 186 patients identified, 87% received sunitinib 50 mg and 88% were on TS; 99 patients continued TS and 87 patients were switched to AS. AEs included fatigue (47%), diarrhea (24%), and hand-foot syndrome (26%). Median time on treatment was 14.9 months in AS patients vs 4.2 months. Median overall survival was 32.9 months vs 18.5 months. ECOG PS≥2 and ≥2 mets were associated with decreased OS. MSKCC intermediate vs poor and AS were associated with improved OS by multivariate regression.
Conclusion: AS sunitinib significantly prolonged outcomes and was predictive of OS. More study is needed of alternate dosing schemes.

Clinical activity and safety of anti-programmed death-1 (PD-1) (BMS-936558/MDX-1106/ONO-4538) in patients with previously treated, metastatic renal cell carcinoma (mRCC). McDermott DF, Drake CG, Sznol M, et al.

Summary: BMS-936558 is a monoclonal antibody that blocks the PD-1 co-inhibitory receptor expressed by activated T cells. Patients were treated with this agent IV q2weeks at 10 mg/kg initially. Patients received up to 12 cycles (4 doses/cycle) of treatment or until unacceptable toxicity, confirmed progressive disease or complete response; 34 patients had been treated as of February 2012. Median duration of therapy was 32 weeks. The incidence of grade 3-4 related adverse events was 18% and included hypophosphatemia (6%), elevated ALT (3%), and cough (3%); no drug-related deaths occurred among mRCC patients. Clinical activity was observed at both doses. Two patients had a persistent reduction in target lesion tumor burden in the presence of new lesions and were not considered responders. There were responses in all sites of disease.
Conclusion: BMS-936558 is well tolerated and has durable clinical activity in patients with previously treated mRCC. Additional long-term follow-up will be reported.

Tivozanib pharmacokinetic (PK)/pharmacodynamic (PD) analysis of blood pressure and soluble vascular endothelial growth factor receptor 2 (sVEGFR2) in patients with advanced renal cell carcinoma (RCC). Nosov DA, Motzer RJ, Loewy J, et al.

Summary: PK, BP, and sVEGFR2 data from tivozanib-treated patients from a phase 2 and a phase 3 study were pooled; patients were treated with tivozanib 1.5 mg daily for 3 weeks followed by 1 weeks rest (4-week treatment cycle) in each study. BP was measured at 9.4 days, and a maximal and on Cycle 1 Day 15 (C1D15), C2D1, and C3D1 in the phase 2 and 3 studies. Models of drug exposure as predictors of longitudinal changes in BP or sVEGFR were constructed. There was a statistically significant median 5 mm Hg increase in diastolic BP on C1D15, with similar increases noted on C2D1. There was a curvilinear decrease in sVEGFR2 with time. An Emax model vs time showed a half-maximal effect occurring in 19.4 days and a maximal 53% decrease in sVEGFR. There was a significant effect of Cavg on Emax: for every 10 ng/mL increase in Cavg; sVEGFR and outcome are being explored.
Conclusion: PK/PD data with tivozanib showed a median increase in diastolic BP of 5 mm Hg on C1D15 and C2D1. Levels of serum sVEGFR decreased significantly with time and the effect size increased with tivozanib exposure. These relationships and outcome are being further explored.

Urine biomarkers to diagnose renal cell carcinoma. Morrissey JJ, Kharasch Ed.

Summary: Urinary levels of the angiogenic-associated protein aquaporin-1 (AQP-1) and a lipid droplet-associated protein adipophilin (ADFP) have been found to be sensitive and specific biomarkers to detect asymptomatic clear cell or papillary kidney cancer. These authors developed an ELISA for AQP-1 to test urine samples from 32 patients with clear cell or papillary kidney cancer undergoing nephrectomy and 43 control patients undergoing surgery for non-kidney related reasons. Of the 32 patients with kidney cancer, 23 had T1a tumors and a median urine AQP-1 concentration of 13.1 ng/mg Cr compared to a median concentration of 0.8 ng/mg Cr for all 43 controls, a significant 16-fold increase ($P < 0.001$). In the 25 patients in whom a post-surgical urine was obtained, there was a significant 86% reduction in the urine AQP-1 concentration.
Conclusion: Measuring urinary AQP-1 concentrations provides a low-cost, noninvasive means of screening patients to identify those with kidney cancer without interference from underlying non-cancerous kidney diseases.

Role of stereotactic body radiotherapy in the management of non-surgical patients. Zeeck K, Rao G, Luckenbough A, et al.

Summary: This is a retrospective review of patients with rapidly growing renal masses who underwent stereotactic body radiotherapy (SBRT) between 2010 and 2011. Patients received a single fraction 15 Gy dose of SBRT and CT scans were done at follow-up at the Roswell Park Cancer Institute. Average patient age was 76; renal mass size at diagnosis was 3.8 cm; average mass growth rate was 3.0 cm/year. Imaging closest to treatment date revealed a tumor size of 5.1 cm. Results showed that ¾ of patients had a decrease in tumor size after SBRT. Among responding patients, at an average follow-up of 16.3 months, the average mass size was 3.8 cm, a 26.3% reduction. The non-responding patient showed a 0.3 cm growth after treatment.
Conclusion: SBRT represents an effective management option in patients with larger, rapidly growing kidney masses. SBRT effects can be observed more than 12 months after treatment.

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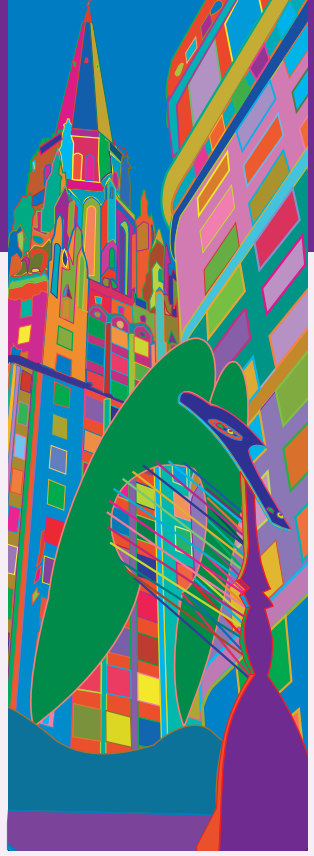

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Next-generation sequencing reveals genomic determinants of long-term response to mTOR inhibitors in patients with advanced RCC. Voss MH, Hakimi AA, Brannon AR, et al.

Summary: A subset of patients with RCC achieves better than the median progression-free survival with mTOR inhibitors. The oncogenomic background for this is unclear. This study used nephrectomy specimens from 6 patients with advanced RCC and ≥ 20 months response to temsirolimus or everolimus. Histologic subtypes were clear cell (n=3) and non-clear cell (n=3). Tumors of 4 long-term responders were found to harbor genomic alterations in genes encoding for key components of the targeted pathway. Loss of function in TSC1 (2 cases) or TSC2 (1 case) and hyperreactivity of mTOR (1 case) explain sensitivity to drug.

Conclusion: Next generation sequencing using pretreatment nephrectomy specimens revealed plausible oncogenomic determinants underlying treatment benefit in 4 of 6 cases. The study implicated 3 different genomic mechanisms of pathway activation, suggesting a foundation for future biomarker development.

Tivozanib versus sorafenib as initial taergeted therapy for patients with advanced renal cell carcinoma: results from a Phase III randomized, open-label, multicenter trial. Motzer RJ, Nosov D, Eisen T, et al.

Summary: Patients with clear-cell RCC, prior nephrectomy, RECIST-defined measurable disease, and Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 were randomized to tivozanib 1.5 mg once daily for 3 weeks followed by 1 week's rest, or sorafenib 400 mg twice daily continuously in a 4-week cycle. Patients were treatment-naïve or received ≤ prior systemic therapy for metastatic disease; patients receiving prior VEGF- or mTOR-targeted therapy were excluded. The primary endpoint was progression-free survival. A total of 517 patients were randomized to the drugs. Median PFS was 11.9 months for tivozanib vs 9.1 months for sorafenib (P=0.042. In the treatment-naïve stratum the median PFS was 12.7 months for tivozanib vs 9.1 months for sorafenib. The objective response rate was 33% for tivozanib vs 23% for sorafenib (P=0.014. The most common AE was hypertension (tivozanib 46%/26% vs sorafenib 54%/17%). Overall survival data have not yet been determined.

Conclusion: Tivozanib demonstrated significant improvement in PFS and ORR vs sorafenib as initial targeted treatment for advanced RCC. Tivozanib was well tolerated with low incidences of fatigue, diarrhea, myelosuppression, and hand-foot syndrome.

Detailed comparison of the safety of tivozanib versus sorafenib in patients with advanced/metastatic renal cell carcinoma (mRCC) from a phase III trial. Eisen T, Sternberg CN, Tomczak P, et al.

Summary: Patients were randomized1:1 to tivozanib 1.5 mg once daily for 3 weeks followed by 1c week's rest, or sorafenib 400 mg twice daily continuously in a 4-week cycle. AEs were recorded until 30 days after last study dose. BP was measured on Days 1 and 15, Day 1 of subsequent cycles, end of treatment, and at 30-day follow-up. Tivozanib-arm patients (175) had fewer drug-related AEs than sorafenib-arm patients (214). Hypertension was the most frequent tivozanib-related AE but was easily managed with standard antihypertensives. Fewer tivozanib-arm patients had Grade ≥3 drug-related AEs than sorafenib-arm patients. Tivozanib-arm patients required fewer overall dose reductions than sorafenib-arm patients, 36 (13.9%) vs 114 44.4%.

Table.

	Tivozanib (n=259)		Sorafenib (n=257)	
	n (%)		n (%)	
AE	All Grades	Grade ≥3	All Grades	Grade ≥3
Hypertension	109 (42.1)	61 (23.6)	79 (30.7)	39 (15.2)
Dysphonia	47 (18.1)	–	11 (4.3)	–
Diarrhea	47 (18.1)	5 (1.9)	71 (27.6)	15 (5.8)
Hand-foot syndrome	34 (13.1)	5 (1.9)	137 (53.3)	43 (16.7)
Fatigue	28 (10.8)	7 (2.7)	28 (10.9)	7 (2.7)
Alopecia	6 (2.3)	–	53 (20.6)	–
Discontinuations	11 (4.2)	–	14 (5.4)	–

Conclusion: Patients receiving tivozanib had more hypertension and dysphonia but less diarrhea, hand-foot syndrome, alopecia, and discontinuations than sorafenib-treated patients. Tivozanib-arm patients also had fewer overall dose reductions. Thus, tivozanib is well tolerated in patients with mRCC. KCJ

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Efficacy endpoint	AE at any time point HR (95% CI)	P*	AE by the 12-wk landmark HR (95% CI)	P*
HTN during treatment				
PFS	0.291 (0.220–0.399)	<0.0001	–	NS
OS	0.296 (0.237–0.427)	<0.0001	0.654 (0.511–0.838)	0.0008
HFS during treatment				
PFS	0.750 (0.595–0.945)	0.0148	–	NS
OS	0.578 (0.437–0.766)	0.0001	0.674 (0.462– 0.985)	0.0415
A/F during treatment				
PFS	0.491 (0.375–0.644)	<0.0001	–	NS
OS	0.720 (0.541–0.959)	0.0245	–	NS

NS = not significant.
*Wald chi-square test.

FDA approves further development of Redectane®, new imaging test for RCC

MUNICH—A clear cell renal cell carcinoma (ccRCC) imaging test has moved c loser to approval by the FDA. A confirmatory diagnostic performance trial was accepted by the FDA instead of an outcomes-based study for Redectane, a new diagnostic test developed by Wilex AG. . The FDA accepted the positive vote of the Oncologic Drugs Advisory Committee (ODAC) regarding the clinical usefulness of the imaging test which identifies ccRCC within the kidney of patients with an indeterminate renal mass. Wilex and the FDA agreed that Wilex will conduct a second diagnostic performance trial instead of an outcomes-based study (i.e. a trial that studies patient outcomes such as survival) that the FDA had previously required. The FDA does, however, require a second trial to confirm the diagnostic performance and safety of Redectane®. WILEX assumes that approval can be expected after successful conclusion of this second trial.

Redectaane is the radioactively labelled form of the antibody Girentuximab. The labelled antibody targets ccRCC and accumulates in the tumor tissue. This accumulation can be visualised by means of positron emission tomography (PET). REDECTANE may be used during diagnostic work up to detect ccRCC in patients with renal masses. At present, only histopathology results after surgery can determine whether the tumour is benign or malignant. As ccRCCs are associated with an aggressive phenotype their identification may help guide appropriate therapeutic management.

Phase 3 ARISER study with Rencarex fails to meet primary endpoint

MUNICH—Analysis from a phase 3adjuvant trial indicates that Rencarex did not meet its primary endpoint, showing no improvement in median disease free survival (approximately 72 months) compared with placebo. The study conducted by Wilex AG has been called the most comprehensive study in the adjuvant setting conducted in the last 20 years. Rencarex is based on the antibody Girentuximab, which binds to the tumor-specific antigen CAIX—an antigen that is overexpressed in clear cell renal cell carcinomas (ccRCC).

ARISER (**A**djuvant **R**ENCAREX® **I**mmunotherapy trial to **S**tudy **E**fficacy in non-metastasized **R**enal cell carcinoma) is an international, multicenter, randomized Phase 3 trial that examines the efficacy of the antibody in comparison to placebo in the treatment of clear cell renal cell cancer patients following complete or partial surgical removal of the affected kidney in patients with no detectable metastases but at high risk of recurrence. The study enrolled 864 patients who had had prior nephrectomy of primary RCC no later than 12 weeks before study entry with documented clear cell histology. KCJ