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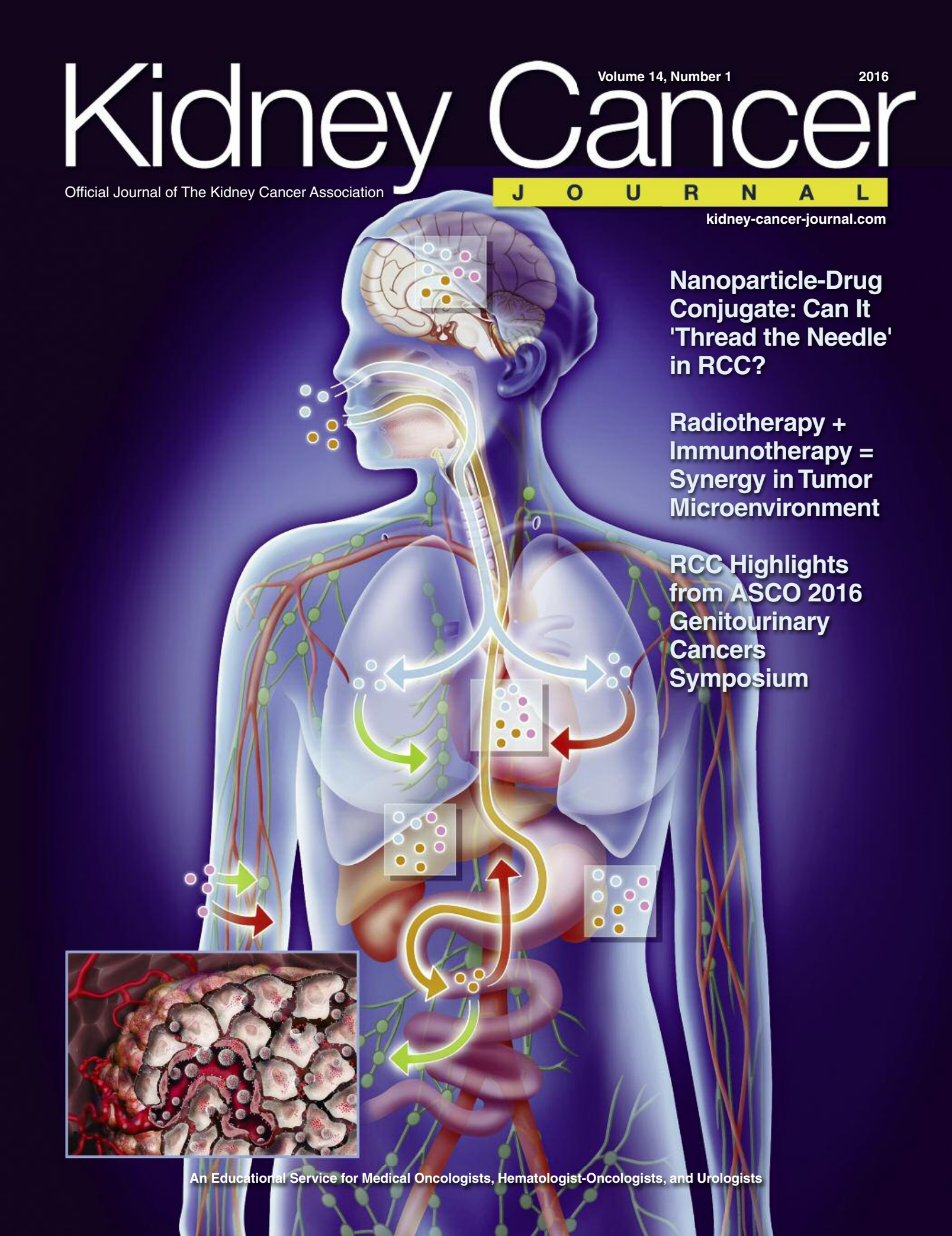


Nanoparticle-Drug Conjugate: Can It 'Thread the Needle' in RCC?

Radiotherapy + Immunotherapy = Synergy in Tumor Microenvironment

RCC Highlights from ASCO 2016 Genitourinary Cancers Symposium

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

Important Safety Information and Indication

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

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

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

Cardiac failure has been observed and can be fatal. Monitor for signs or symptoms of cardiac failure throughout treatment with INLYTA. Management of cardiac failure may require permanent discontinuation of INLYTA.

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

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

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

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

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

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

Inlyta®
axitinib 1mg and 5mg tablets
CONTINUE THE FIGHT

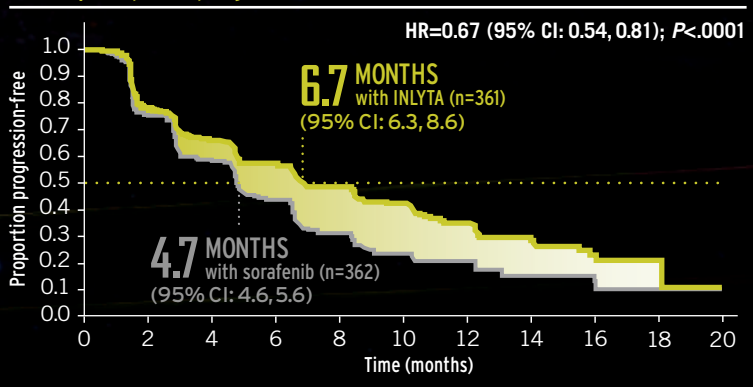
GIVE THEM A FIGHTING SECOND CHANCE

INLYTA IS INDICATED FOR THE TREATMENT OF ADVANCED RCC AFTER FAILURE OF ONE PRIOR SYSTEMIC THERAPY.

INLYTA—the ONLY approved treatment option to demonstrate superior PFS vs a TKI, sorafenib, in a phase 3 trial for 2nd-line mRCC*

*Based on MEDLINE® literature review for phase 3 trials in mRCC as of February 2016. TKI=tyrosine kinase inhibitor.

Primary endpoint: progression-free survival (PFS)



Data are from a multicenter, open-label, phase 3 trial of 723 patients with mRCC after failure of 1st-line therapy (sunitinib-, temsirolimus-, bevacizumab-, or cytokine-containing regimen [54%, 3%, 8%, and 35% of patients in each of the treatment arms, respectively]). Patients were randomized 1:1 to either INLYTA 5 mg twice daily (n=361) or sorafenib 400 mg twice daily (n=362), with dose adjustments allowed in both groups. Primary endpoint was PFS. Secondary endpoints included objective response rate, overall survival, and safety and tolerability.[1,2]

Axitinib has a National Comprehensive Cancer Network® (NCCN®) category 1 recommendation as a subsequent therapy option, after either a TKI or a cytokine therapy in patients with advanced predominantly clear-cell RCC.[3]

INLYTA has been approved by the FDA for the treatment of advanced renal cell carcinoma (RCC) after failure of one prior systemic therapy.

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 (55% vs 53%), hypertension (40% vs 29%), fatigue (39% vs 32%), decreased appetite (34% vs 29%), nausea (32% vs 22%), dysphonia (31% vs 14%), hand-foot syndrome (27% vs 51%), weight decreased (25% vs 21%), vomiting (24% vs 17%), asthenia (21% vs 14%), and constipation (20% vs 20%).

The **most common (≥10%) grade 3/4 AEs** occurring in patients receiving INLYTA (vs sorafenib) were hypertension (16% vs 11%), diarrhea (11% vs 7%), and fatigue (11% vs 5%).

The **most common (≥20%) lab abnormalities** occurring in patients receiving INLYTA (all grades, vs sorafenib) included increased creatinine (55% vs 41%), decreased bicarbonate (44% vs 43%), hypocalcemia (39% vs 59%), decreased hemoglobin (35% vs 52%), decreased lymphocytes (absolute) (33% vs 36%), increased ALP (30% vs 34%), hyperglycemia (28% vs 23%), increased lipase (27% vs 46%), increased amylase (25% vs 33%), increased ALT (22% vs 22%), and increased AST (20% vs 25%).

Indication

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

Please see Brief Summary on the following pages.

March 2016

Pfizer U.S. Pharmaceuticals

References: 1. Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. *Lancet*. 2011;378(9807):1931-1939. **2.** Data on file. Pfizer Inc, New York, NY. **3.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Kidney Cancer V.2.2016. © National Comprehensive Cancer Network, Inc. 2015. All rights reserved. Accessed January 28, 2016. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

mRCC=metastatic renal cell carcinoma; NCCN=National Comprehensive Cancer Network.

INLYTA® (AXITINIB) TABLETS FOR ORAL ADMINISTRATION

Initial U.S. Approval: 2012

Brief Summary of Prescribing Information

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

DOSAGE AND ADMINISTRATION

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

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

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

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

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

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

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

DOSAGE FORMS AND STRENGTHS

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

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

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DRUG INTERACTIONS

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

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

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

USE IN SPECIFIC POPULATIONS

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

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

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

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

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

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

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

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

No dosage adjustment is required in elderly patients.

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

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

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

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

OVERDOSAGE

There is no specific treatment for INLYTA overdose.

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

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

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

NONCLINICAL TOXICOLOGY

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

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

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

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

PATIENT COUNSELING INFORMATION

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

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

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

Rx only August 2014

About the Cover
A conceptual rendering of mechanisms for a nanoparticle-drug conjugate in renal cell carcinoma. Cut-away computer illustration shows nanoparticles (spheres) containing cytotoxic drugs, targeting tumor cells in kidney. Phase 2 trial is currently underway to determine efficacy of delivering a payload of chemotherapy and bevacizumab to RCC cells. (Copyright, Photo Researchers)

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KCJ EDITOR'S MEMO

Chemotherapy and radiation—ineffective in RCC. Think again.

True or False: Chemotherapy and radiation are generally considered ineffective treatment approaches in renal cell carcinoma (RCC). The knee-jerk response would be "true," and if the question appeared on a CME post-test, for example, the response would no doubt be considered correct, since the prevailing opinion about these two modalities is that they *are* largely ineffective, certainly ineffective compared to the standard of care use of targeted agents. However, if the question were slightly reworded, "chemotherapy and radiation are being reconsidered as effective treatment options in RCC," there would be reason to think again about how one responds. In this case, the correct response again might be "True," contrary to conventional wisdom.

No one is saying that we are witnessing a tectonic shift in the treatment paradigm. This is far from the case. But there is an undercurrent in the literature that compels us to revisit our conventional views about chemotherapy and radiation in RCC. It is not that the modalities as monotherapy are generating new hypotheses but when used in combination with another agent or vehicle to deliver treatment, chemotherapy and radiation are getting a fresh look.

Consider one hypothesis from a recent report that serves as a cutting edge for reevaluating radiation. The authors suggest that stereotactic body radiotherapy (SBRT) and interleukin-2 therapy could provide potential benefit. The hypothesis is that radiation increases tumor antigen release and changes the tumor microenvironment such that the immune effects of IL-2 are significantly more effective in melanoma and RCC.

None of the studies suggest that radiotherapy has a role by itself (except in specific circumstances involving oligometastatic disease , its use in treating CNS metastasis, or for palliation). This is especially true in view of new data on immunotherapy using checkpoint inhibitors. As checkpoint blockade gets mainstream attention—due to striking and durable clinical responses in some patients with metastatic disease—there is more interest in the biological and mechanistic rationale behind combining radiation with checkpoint blockade immunotherapy. The emphasis of studies so far continues to be on fractionated and not single dose radiotherapy. The report in this issue of the *Kidney Cancer Journal* brings everyone up to date

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Kidney Cancer Journal Author Guidelines

Scope of Manuscripts

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

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

Manuscript Submission

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

All material reproduced from previously published, copyrighted material should contain a full credit line acknowledging the original source. The author is responsible for obtaining this permission.

Contact information

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

Peer Review and Editing

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

Conflict of Interest

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

Manuscript Preparation

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

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

References

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

Copyright

Essential Peer-Reviewed Reading in Kidney Cancer

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

Multilevel Genomics-Based Taxonomy of Renal Cell Carcinoma. Chen F, enbabao lu Y, Ciriello G, et al. *Cell Rep*. 2016;14: 2476–2489.

Summary: On the basis of multidimensional and comprehensive molecular characterization (including DNA methalylation and copy number, RNA, and protein expression), tis study classified 894 renal cell carcinomas (RCCs) of various histologic types into nine major genomic subtypes. Site of origin within the nephron was one major determinant in the classification, reflecting differences among clear cell, chromophobe, and papillary RCC. Widespread molecular changes associated with TFE3 gene fusion or chromatin modifier genes were present within a specific subtype and spanned multiple subtypes. Differences in patient survival and in alteration of specific pathways (including hypoxia, metabolism, MAP kinase, NRF2-ARE, Hippo, immune checkpoint, and PI3K/AKT/mTOR) could further distinguish the subtypes.

Conclusion: Immune checkpoint markers and molecular signatures of T cell infiltrates were both highest in the subtype associated with aggressive clear cell RCC. Differences between the genomic subtypes suggest that therapeutic strategies could be tailored to each RCC disease subset.

A Rare Finding of a BRAF Mutation in Renal Cell Carcinoma with Response to BRAF-Directed Targeted Therapy. Banerjee N, Sachdev E, Figlin RA. *Cureus*. 2016; Jan 6; 8(1):e449.

Summary: Whole exome sequencing can identify somatic mutations in malignant tumors and allow for personalized and novel treatment of common malignancies. Mutations in the BRAF gene are rare in renal cell carcinoma, and thus, BRAF inhibitors are not considered standard in the treatment of these cancers. Here, the authors report a case of a patient with a rare BRAF-mutated metastatic renal cell carcinoma who obtained a good clinical response to BRAF inhibition.

Conclusion: This case underscores the value of precision medicine in an era of rapidly evolving therapeutics for malignancies.

Positive Surgical Margins Increase Risk of Recurrence after Partial Nephrectomy for High-Risk Renal Tumors. Shah PH, Moreira DM, Okhunov Z, et al. *J Urol*. 2016 Feb 18; S0022-5347(16)00352-9. doi: 10.1016/j. juro. 2016.02.075 [Epub ahead of print]

Summary: The clinical significance of positive surgical margins after partial nephrectomy remains controversial. Association between positive margin and risk of disease recurrence among patients with clinically localized renal neoplasms undergoing partial nephrectomy was evaluated. A retrospective multi-institutional review of 1240 patients undergoing partial nephrectomy for clinically localized renal cell carcinoma between 2006 and 2013 was performed. Recurrence-free survival was estimated using the Kaplan-Meier method and evaluated as a function of positive surgical margin with log-rank test and Cox models adjusting for tumor size, grade, histology, pathologic stage, focality, and laterality. The relationship between positive margin and risk of relapse was evaluated independently for pathologic high-risk (pT2-3a or Fuhrman grades III-IV) and low-risk (pT1 and Fuhrman grades I-II) groups. Positive surgical margin was encountered in 97 (7.8%) patients. Recurrence developed in 69 (5.6%) patients over a median follow up of 33 months, including 37 (10.3%) patients with high-risk disease (e.g. pT2-pT3a or Fuhrman grade III-IV). Positive margin was associated with increased risk of relapse on multivariable analysis (P=0.03), but not with site of recurrence. In a stratified analysis based on pathological features, positive surgical margin was significantly associated with a higher risk of recurrence among patients considered high-risk (P<0.001) but not low-risk (P=0.647).

Conclusion: A positive surgical margin after partial nephrectomy increases risk of disease recurrence, primarily in patients with adverse pathologic features.

Overall Survival Endpoint in Oncology Clinical Trials: Addressing the Effect of Crossover - The Case of Pazopanib in Advanced Renal Cell Carcinoma. Diaz J, Sternberg CN, Mehmud F, et al. *Oncology*. 2016;90(3): 119-26. doi: 10.1159/000443647. Epub 2016 Feb 23.

Summary: This study identified the issues of using overall survival (OS) as a primary endpoint in the presence of crossover and the statistical analyses available to adjust for confounded OS due to crossover in oncology clinical trials. An indirect comparison was conducted between pazopanib and sunitinib in advanced renal cell carcinoma. Statistical adjustment methods were used to estimate the true comparative effectiveness of these treatments. Recently, a head-to-head trial comparing pazopanib and sunitinib was completed. This provided the opportunity to compare the OS treatment effect estimated for pazopanib versus sunitinib using indirect comparison and statistical adjustment techniques with that observed in the head-to-head trial. Using a rank-preserving structural failure time model to adjust for crossover in the pazopanib registration trial, the indirect comparison of pazopanib versus sunitinib resulted in an OS hazard ratio

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

Large genomic study expands identification of RCC subtypes

HOUSTON—Analyzing 894 primary renal cell carcinomas, a Baylor College of Medicine team has zeroed in on more specifically identifying subtypes of kidney cancer. A comprehensive molecular analysis resulted in nine subtypes defined by systematic analysis of five genomic data platforms. Each major histologic type represents substantial molecular diversity.

The team discovered that what have historically been considered three major types of kidney cancer according to their characteristics under the microscope, could be further distinguished into nine major subtypes through molecular analyses. Each subtype was unique in terms of altered molecular pathways and patient survival. This study made use of data from *The Cancer Genome Atlas (TCGA)*.

Researchers found that the immune checkpoint pathway was most active in a subtype of clear cell kidney cancer that is typically very aggressive. "Not all patients have this pathway activated but molecular analysis would allow us to identify those patients that represent the best candidates for receiving therapies that target that pathway specifically," according to Chad Creighton, MD, associate professor of medicine and member of the Dan L Duncan Comprehensive Cancer Center Division of Biostatistics at Baylor College of Medicine, who led the study. "If we have this information, then we may have an idea of what would work better for the patient. The molecular information can potentially help guide better decisions for treating each patient."

Using an extended dataset of samples not present in the initial TCGA marker studies, the authors were able to make novel findings in this present study, through comparisons and contrasts across the major histologic types of RCC. For a full report see Chen et al. Multilevel Genomics-Based Taxonomy of Renal Cell Carcinoma. *Cell Reports*. 2016; 14:2476–2489.

New data on nanoparticle technology presented on solid tumors

WALTHAM, MA—Results from an ongoing study of nanoparticle-drug conjugates suggest potential antitumor activity. CRLX301 is an NDC designed to concentrate in tumors and slowly release its payload, docetaxel, inside the cancer cells while sparing healthy tissue. An abstract, entitled "A phase 1 study of CRLX301, a novel Nanoparticle-Drug Conjugate (NDC) containing docetaxel, in patients with refractory solid tumors," was presented during a poster session at the 14th International Congress on Targeted Anticancer Therapies in March in Washington, DC. *(See related story in this issue on nanoparticle technology and renal cell carcinoma.)*

"There were several important outcomes from the dose-escalation portion of this study, including the determination of the maximum tolerated dose (MTD) on a once-every-three-weeks (Q3W) dosing schedule. CRLX301 was generally well tolerated, showed hints of antitumor activity, and exhibited a differentiated pharmacokinetic (PK) profile compared to docetaxel," said Adrian Senderowicz, MD, Senior Vice President & Chief Medical Officer of Cerulean. "These early data suggest that CRLX301 has the potential to be a better-tolerated taxane that could be combined with other cancer treatments to provide better outcomes for patients. As a result of what we learned in Phase 1, we are moving into a Phase 2a, where we will look for further signals of activity."

Highlights from the data include:

- CRLX301 is generally well tolerated. Across all cohorts, reported drug-related adverse events (AEs) were toxicities associated with docetaxel, with no unexpected toxicities. The majority of the AEs were mild to moderate and transient. The most common drug-related AEs of grade ≥3 were neutropenia and hypersensitivity/infusion reaction.
- Hints of clinical activity include (a) a patient with B-RAF mutant adenocarcinoma of unknown primary, previously refractory to vemurafenib that demonstrated clear evidence of tumor shrinkage as evidenced by CT and PET scans and (b) two patients with prolonged stable disease (7 and 16 cycles).
- PK analysis suggests that CRLX301 stays intact in circulation for an extended period of time, resulting in ~100 times greater plasma exposure of the intact NDC relative to published data for docetaxel. Importantly, there was a 20-fold reduction of the maximal concentration (Cmax) of released docetaxel when compared to published data of docetaxel.

Core-needle biopsy may enhance diagnosis in selected RCC patients

WAIKOLOA, HI—Adding core-needle biopsy may help improve outcomes for some patients with RCC, according to a

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Threading the Needle With Nanoparticle Technology to Improve the Therapeutic Index in RCC

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Kidney Cancer Journal
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The parameters and goals of a new Phase 2 trial, now fully accrued, are described. Exploring the use of nanoparticle technology in renal cell carcinoma, this trial could suggest a new approach for treatment of patients who are refractory to earlier lines of therapy.

Enrollment in a randomized Phase 2 trial evaluating a dose-intensive schedule for a nanoparticle-drug conjugate, CRLX101, in combination with bevacizumab (Avastin) in third- and fourth-line relapsed renal cell carcinoma (RCC) is now complete. The trial has enrolled all 110 patients and top-line data are expected later in 2016.

Expectations surrounding this trial are high in view of positive data gained in a phase 1b/2 study in which the nanoparticle conjugate was also evaluated and showed promise for extending progression-free survival (PFS). The Phase 2 trial compares CRLX101 in combination with bevacizumab to investigator's choice of standard of care (SOC) in patients with RCC who have received two or three prior lines of therapy.

The primary endpoint is investigator-assessed progression free survival (PFS) according to Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1. PFS also will be evaluated by blinded independent radiological review. Other secondary endpoints include overall response rate, duration of response and overall survival. The trial is sized to show a 2.3 month improvement over an expected 3.5 month median PFS for standard of care with a hazard ratio of 0.6, meaning that the trial is expected to show whether CRLX101 plus bevcizumab provides a 40% improvement in PFS over available third- and fourth-line treatments.

One of the goals of the Phase 2 trial is to explore whether an increase in intensity with a q 2 weeks dosing regimen may enhance the therapeutic index, enabling additional registration strategies using this novel regimen. The nanoparticle has been studied in more than 350 patients with bi-weekly dosing in multiple tumor types when given as monotherapy and in combination with other therapies.[1]

CRLX101 is designed to concentrate in tumors and slowly release its anti-cancer payload, camptothecin, inside tumor cells. CRLX101 inhibits topoisomerase 1 (topo 1), which is involved in cellular replication, and also inhibits hypoxia-inducible factor-1 (HIF-1) and HIF-2 , considered a master regulator of cancer cell survival mechanisms. Camptothecin is a potent topoisomerase 1 inhibitor that was too toxic to develop clinically; however, the rationale for using it is that CRLX101 appears to reduce the toxicities associated with camptothecin, while increasing the payload concentration in tumors. The FDA has granted CRLX101 Orphan Drug designation for the treatment of ovarian cancer and Fast Track designation in combination with bevacizumab in metastatic RCC.

Tumor cells are genetically diverse and can rapidly resist and ultimately overcome a single-agent therapy by modulating various adaptive pathways; however, if multiple drugs simultaneously shut down multiple adaptive pathways, there is a greater chance of achieving disease responses for an extended period of time. Radiotherapy and anti-angiogenic drugs exacerbate the hypoxic tumors. Tumors respond to the hypoxia by upregulating HIF-1 , which subsequently activates multiple adaptive pathways to help promote tumor cell survival in low-oxygen conditions leading to treatment failures. By inhibiting HIF-1, CRLX101 may help radiotherapy and/or anti-angiogenic drugs to be more effective in killing tumor cells.

At the 2015 meeting of the American Society of Clinical Oncology (ASCO), investigators delineated the challenges of treating metastatic RCC and provided additional information on the trial's protocol. Voss et al[2] reported that up to 30% of patients with RCC present with metastatic disease and 5-year survival among these patients[2] is less than 10%. VEGF-targeted and mTOR in-

Keywords: nanoparticle-drug conjugate, renal cell carcinoma, CRLX101, chemotherapy, bevacizumab.

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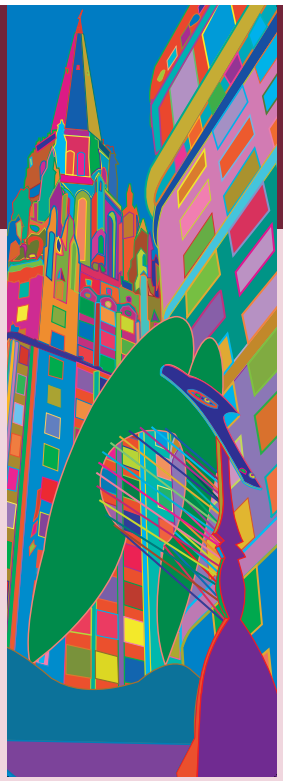

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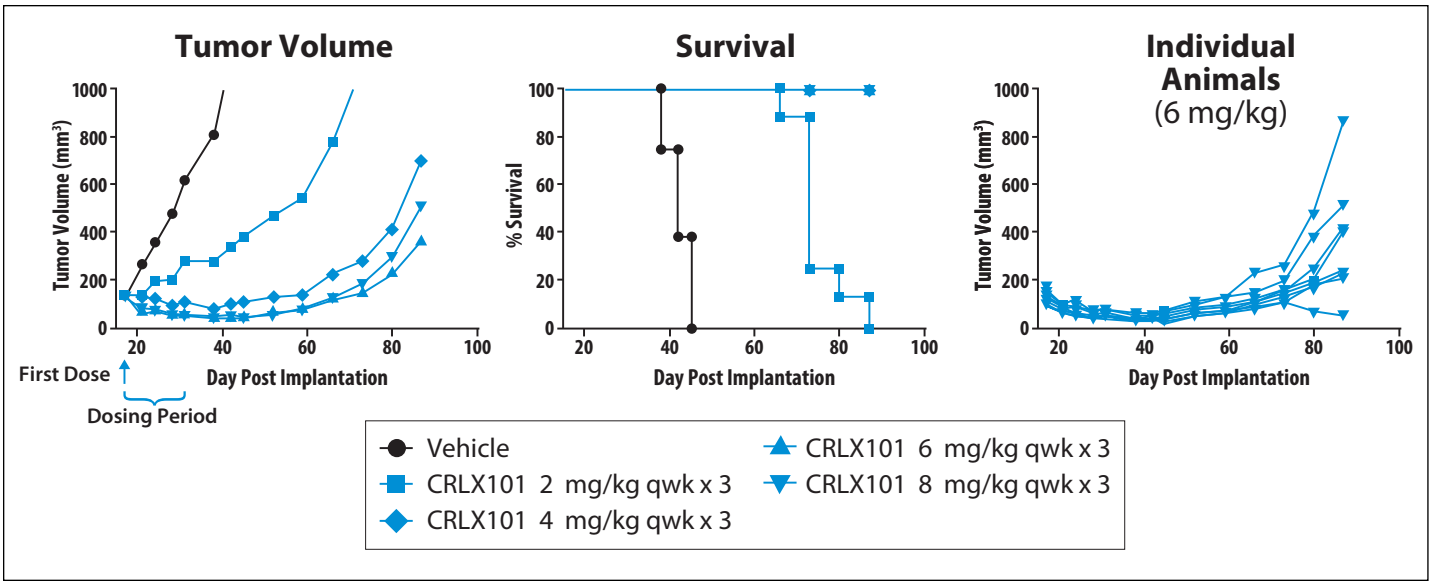

Figure 1. Caki-1 Renal Xenograft Tumor Growth Delay Study.

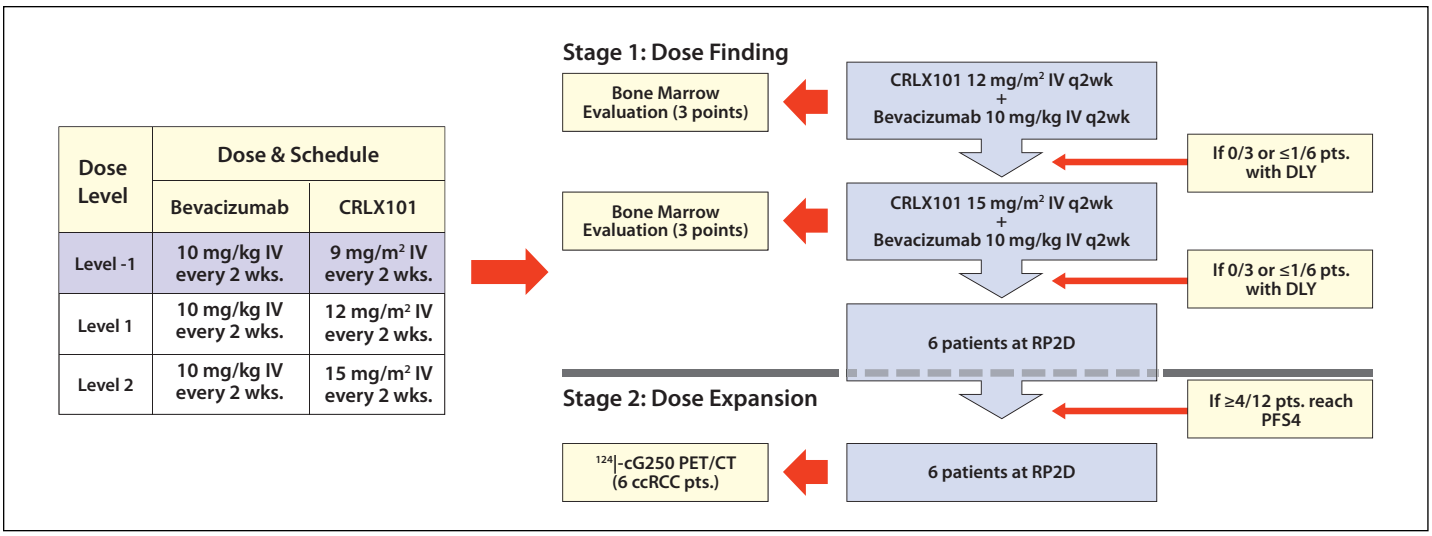

Figure 2. Advanced Renal Cell Carcinoma Schema. (University of Pennsylvania)

hibiting drugs constitute standard of care in this setting but anti-tumor effects are generally short-lived and there exists a pressing need for new therapeutic strategies. Among patients with tumors progressing through multiple prior lines of therapy, the GOLD trial[3] reported that sorafenib and the comparator agent dovitinib achieved PFS of approximately 4 months.

Clear cell RCC (ccRCC) accounts for approximately 80% of RCC and is characterized by high levels of HIF-1 and HIF 2 alpha, providing an ideal clinical setting in which to evaluate potential synergy between CRLX101 and the VEGF inhibitor bevacizumab.[2] Phase 2 data presented separately at ASCO highlighted notable signals of RCC activity for this combination with objective response rate (ORR) and median progression free survival (mPFS) exceeding 20% and 9 months, respectively.

Conducted at approximately 40 US cancer centers, the new Phase 2 randomized clinical trial has enrolled patients with advanced, unresectable metastatic RCC who have completed 2 or 3 prior regimens of therapy.[4] The primary endpoint will compare PFS among 90 clear cell-cc RCC patients treated with concurrently administered CRLX101 + bevacizumab vs SOC (any approved agent per investigator choice not previously used in the same patient). Statistical power is set at 80% to detect an increase in median (**Figures 1, 2, 3**) PFS from 3.5 mos. to 5.8 mos. (HR~0.6). Secondary/exploratory end-points include overall survival, ORR, safety, pharmacokinetics, and plasma biomarkers of efficacy. Additionally, 20 patients with non-ccRCC histology will be evaluated independently. Clinical trial information can be found at NCT02187302.

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1. Data on file. http://ceruleanrx.com/platform-pipeline/crlx101.php.
2. Voss MH, Coates A, Garmey EG, et al. Randomized phase 2 study to assess the safety and efficacy of CRLX101 in combination with bevacizumab in patients (pts.) with metastatic renal cell carcinoma (RCC) versus standard of care (SOC). *J Clin Oncol*. 2015;33, (suppl; abstr TPS4579).

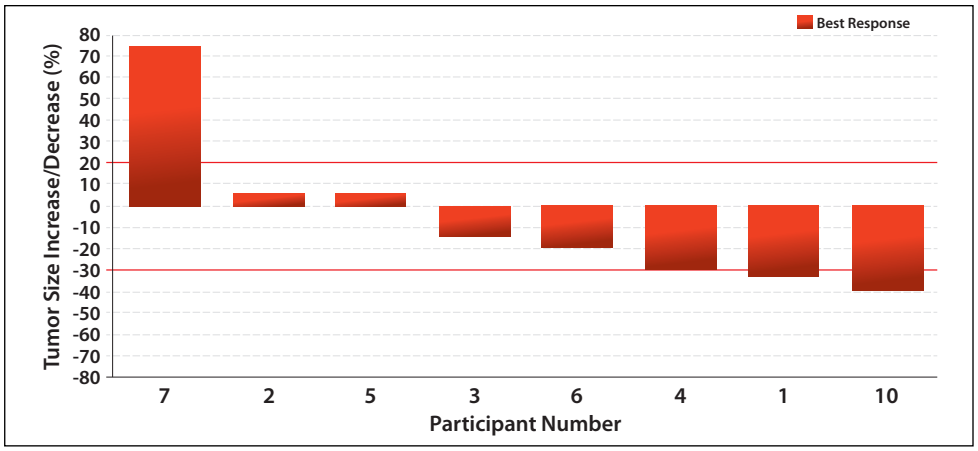

Figure 3. Best Response per RECIST Renal Cell Carcinoma

3. Motzer RJ, Porta C, Vogelzang NJ, et al. Dovitinib versus sorafenib for third-line targeted treatment of patients with metastatic renal cell carcinoma: an open-label, randomised phase 3 trial. *Lancet Oncol.* 2014; 15:286-296.
4. CRLX101 in Combination With Bevacizumab for Metastatic Renal Cell Carcinoma (mRCC) Versus Standard of Care (SOC) https://clinicaltrials.gov/show/NCT02187302. KCJ

KCJ INTERVIEW

Inside the Pipeline: A Leading Investigator Examines the Potential of a New Platform and Drug Delivery Vehicle

In this interview, Nicholas J. Vogelzang, MD, FASCO, FACP, discusses the implications of an open-label, dose-escalation study in patients with advanced solid tumor malignancies who will undergo treatment with CRLX101, a nanoparticle-drug conjugate. Dr Vogelzang is a medical oncologist with Comprehensive Cancer Centers of Nevada, Las Vegas, Nevada. He serves as Medical Director of the Research Executive Committee and Associate Chair of the Developmental Therapeutics and Genitourinary Committees for US Oncology Research.

Q: Please tell us about the trial you are participating in that evaluates the use of nanoparticle technology in kidney cancer.

Dr Vogelzang: The trial fully accrued 110 patients on 11/5/15 but we do not have any results yet. The idea behind the trial is that CRLX101, a nanoparticle linked to Camptosar® (irinotecan CPT-11) is a potent inhibitor of topoisomerase-1 (topo-1). The data that Cerulean has generated now suggests that irinotecan inhibits not only topo-1 but also hypoxia inducible factor-1α (HIF-1α) and hypoxia inducible factor-2 alpha (HIF-2α): HIF-1α is a master regulator of several key cancer survival mechanisms and was previously undruggable. HIF-1α up-regulates cancer cell survival pathways such as drug resistance, cancer stem cell formation, and metastasis formation. HIF-1α levels increase in the hypoxic, or oxygen deprived, conditions that are present in solid tumors. HIF-2α is upregulated specifically in many but nor all renal cancers, specifically those with VHL mutations.

Furthermore, many anti-neoplastics such as radiation therapy and anti-angiogenesis drugs reduce oxygen levels in solid tumors, thereby driving up HIF-1α even further. In animal models, CRLX101 inhibits HIF-1α alone and in combination with anti-angiogenesis drugs. The 30nm nanoparticle holding irinotecan is small enough to pass through the tumor vasculature. Then the nanoparticle is taken up by the tumor cell via macro-pinocytosis. In cell lines and cancer xeno-grafts the cell is killed more effectively than with irinotecan alone.

Q: Are you saying that the nanoparticle containing chemotherapy is too large to enter other non-tumor cells?

Dr Vogelzang: That is always the question: how selective is the nanoparticle uptake? It's like anything else in oncology in that there is a therapeutic index. This is not a fully benign molecule because there is already evidence that the nanoparticle/irinotecan irritates the lining of the bladder causing cystitis. So Cerulean recommends that each dose be given with 1 liter of fluid to prevent the cystitis probably resulting from direct bladder toxicity. The therapeutic ratio is thus not ideal, there are side effects. That is exactly why some of us are a bit skeptical.

Q: What are the challenges of devising a strategy for RCC using the traditional chemotherapies? Are there specific mechanisms of resistance that need to be addressed?

Dr Vogelzang: In the past the standard chemotherapy drugs that were tested for their ability to induce responses in kidney cancer were all essentially negative. There was really no effective drug. The exceptions were the fluoropyrmidines and the purines. 5FU and gemcitabine had some activity and even to this day there are some patients I treat with highly refractory kidney cancer who receive 5FU and gemcitabine. The reason we have not been able to give the other drugs effectively is that these cancer cells are derived from the proximal tubular epithelium. These cells are capable of withstanding harsh conditions of urinary acidity and urinary toxins. The proximal tubule epithelium has a very high resistance to drugs. They show a high expression of P glycoproteins which are transport proteins designed to excrete drugs from the proximal tubule epithelium. The word I use to describe these cells is that they are like "leather." If a cancer develops in the proximal tubule of kidney it seems logical that this kidney cancer itself shares these characteristics. That was borne out in the Cancer Genome Atlas. It showed that some of these tumors have significant overexpression of these transport proteins.

Q: Is it realistic for clinicians to expect some kind of a breakthrough with nanoparticle technology? How much reason is there for a true and significant advance?

Dr Vogelzang: As an analogy I liken the process to a dog barking up a tree. Is there a squirrel up there? Well, probably since dogs can smell it. But can they catch the squirrel? Companies in the hunt for new drugs have to "bark up trees", they have take these gambles to catch the next squirrel. The nanoparticle technology is the next squirrel. The field is rapidly moving along. However, nanoparticles are a delivery system, not a drug. The nano-particle is fully dependent on the effectiveness of the irinotecan in killing the cancer cell.

Q: Is it too early to see where the nanoparticle might find a place in the treatment algorithm?

Dr Vogelzang: It is down the line from what we have now. When drug resistance occurs, patients do not have many other options. At that point the cancer possibly has evolved away from sensitivity to a VEGF or mTOR inhibitor. When the Cerulean trial of CRX-101 started, 3rd line therapy for RCC was an open field. We had just finished the trial of dovitinib vs sorafenib, which was a negative trial. We had a median PFS of 4 months for both drugs. And median survival was 11 months for both drugs.

Q: How different so far has the experience been with CRLX-101?

Dr Vogelzang: In the phase 1b/2 trial, the University of Pennsylvania investigators achieved partial responses and a PFS of about 9 months with the nanoparticle technology in third- and some fourth-line patients. We acknowledge that PFS can be biased by trial selection criteria. We have reexamined that and it looks as if these are fairly typical patients. We also liked the fact that there were patients in the trial who responded who had papillary/ non-clear cell carcinoma. That is a big unmet medical need because the TKIs do not really work in that subset.

Q: Are you screening for these patients as well as part of the protocol moving forward?

Dr Vogelzang: Yes, they were especially allowed to be enrolled. I think the design called for up to 20% of the patients in the trial to be papillary or non-clear cell.

Q: What are you expecting to see from the phase 2 trial that will be encouraging?

Dr Vogelzang: If we get a PFS of 8 or 9 months we would be jumping for joy. If we only get 4 months, we will be disappointed. The other thing that we will be looking for is response. If there are significant objective responses, particularly in the non-clear cell group, that will be encouraging because the non-clear cell histology usually has a response rate that is barely 10%. So the bar for success in non-clear cell is quite low. In terms of design, since the market for non-clear cell is small, the study had to be aimed at both clear and non-clear cell carcinoma.

Q: Are you using RECIST criteria as well?

Dr Vogelzang: That will be a secondary endpoint in the phase 3 trial. The control group will be monotherapy with Avastin. Although Avastin is not considered a highly active drug in later lines of therapy there was a recent report in *Clinical GenitourinaryCancer* (Bevacizumab monotherapy as salvage therapy for advanced clear cell renal cell carcinoma pretreated with targeted drugs, (C-H Lee, A Hotker, MH Voss et al CGC 14:1 p56-62) demonstrating that Avastin as monotherapy in 71 patients (51% treated as 4th or later line of therapy) demonstrated a median OS of 11.5 months and a median PFS of 1.9 months. Nine patients (13%) were on therapy for more than 12 months

Q: What about the side effect profile of the nanoparticle technology?

Dr Vogelzang: The Cerulean molecule plus Avastin does not appear to be more toxic than Avastin alone with the exception of the cystitis noted above.

Q: What about mechanisms? Are you inhibiting hypoxia inducible factor with the nanoparticle?

Dr Vogelzang: That is the theory. CP-11 may inhibit HIF1 and 2 α but it is cytotoxic, too in that it inhibits Topo-1. The CLRX-101 seems to be additive or even potentially synergistic with the TKIs and Avastin

Q: There is so much talk about personalized medicine in cancer. Is this a personalized approach?

Dr Vogelzang: No, it is not personalized. The company has spent a lot of time and effort to discover the mechanism. The hypothesis is that irinotecan has a role to play in HIF1 α and 2 α-positive renal cells. It is a reasonable hypothesis.

Q: It is early in the protocol, but can you speculate on how the treatment algorithm could change if you obtain some positive results?

Dr Vogelzang: It is not likely to be a third-line therapy. It is more likely to be a fourth or fifth line. Patients are likely to be a bit "beaten up" by the time this treatment is given because of other agents tried first. So overall, we still have the TKIs (sunitinib or Pazopanib) as first line, then nivolumab as second line, third line is either Axitinib an mTOR inhibitor or carbozantinib, and fourth line would be an agent not used as third line. I can easily see the nanoparticle plus Avastin coming in as a fourth- fifth line.

Q: In the design of the trial are you accounting for poor prognosis patients, using the Motzer criteria?

Dr Vogelzang: We will stratify patients but it will not be part of the eligibility criteria.

Q: When are you likely to see results and do you have any other observations?

Dr Vogelzang: The goal is to have the phase 2 results presented at a meeting in 2016 or early 2017. You know, there is a conundrum for renal cancer doctors at this point. We have good drugs up to the fifth line. Accrual to this trial will require some discipline. I am not sure if clinical trial investigators will want to give up on the sequence of sunitinib/pazopanib, nivolumab, Axitinib, and cabozantinib. We will need some impressive results from the phase 2 trial to break into that treatment paradigm. KCJ

Emerging Concepts, Preclinical Models Characterize Nanoparticle Delivery Systems Under Study for Treatment of a Range of Tumors

Proponents of nanoparticle technology are touting this platform as a revolutionary advance, perhaps pointing toward a tectonic sift in the way drugs are administered. Numerous articles have appeared and a sampling of these reports chronicles the progress of nanoparticles in cancer therapy, perhaps best described as incremental at this point. Nevertheless, these preclinical and hypothesis-generating studies offer an exciting glimpse of what could loom ahead in cancer treatment.

If nanoparticle technology moves from the bench to the bedside in kidney cancer, its effectiveness will rest on a solid foundation of earlier studies in other cancers that serve as pio- neering efforts in how this approach could become viable. There is an abundant and growing literature, particularly in the last few years, demonstrating how application of the technology could have a sharp impact on clinical decision making.

Nevertheless, like other treatments touted as revolutionary strategies certain to change the paradigm of treatment, nanoparticle technology still needs to be viewed as a cautionary tale, requiring further Phase 3 clinical trials to justify the expectations it has aroused. If therapeutic nanoparticles co-encapsulating multiple types of drugs are more potent against cancer cells, questions arise as to whether they are also more
likely to inflict collateral damage on healthy tissues.[1] In the preclinical trials of renal cell carcinoma, the technology appears to be safe. However, the therapeutic index of nanoparticle technology in various cancers needs to be more clearly delineated and established; and it remains a prime focus of numerous studies seeking to build on the hypotheses generated in a variety of cancers, ranging from colorectal tumors to malignancies in the brain and lungs.

The advantages conferred by nanoparticles are significant. Advances in biocompatible nanoscale drug carriers such as liposomes and polymeric nanoparticles have enabled more efficient and safer delivery of a myriad of drugs. Advantages in nanoparticle drug delivery, particularly at the systemic level, include longer circulation half-lives, improved pharmacokinetics and reduced side effects.[2-4] In cancer treatments, nanoparticles can further rely on the enhanced permeability and retention effect caused by leaky tumor vasculatures for better drug accumulation at the tumor sites.[5] These benefits have made therapeutic nanoparticles a promising candidate to replace traditional chemotherapy, where intravenous injection of toxic agents poses a serious threat to healthy tissues and results in dose-limiting side effects.

A review of recent literature suggests the extent to which nanoparticles could play a role in enhancing the delivery of various combinations of treatment. Although largely preclinical reports, the data presented offer tantalizing information and a platform for future investigation. A study by Fisusi, for example, addressed a key unmet medical need: the fact that the blood brain barrier compromises glioblastoma chemotherapy.[6] High blood concentrations of lipo-philic, alkylating drugs result in brain uptake, but they cause myelosuppression. The hypothesis was that nanoparticles could achieve therapeutic brain concentrations without dose-liET) nano-particles or ethanolic lomustine. The MET formulation significantly increased mice survival times compared to ethanolic lomustine or no treatment: 33.2, 22.5 and 21.3 days. The study concluded that particulate drug formulations improved brain tumor therapy without major bone marrow toxicity.

There are numerous studies, many representing truly cutting edge technologies, exploring how nanoparticles could potentially be integrated into delivery systems carrying payloads of immunotherapy or chemotherapy. In one report, for example, Lee et al[7] devised a delivery system for nanoparticles with chemotherapy for colorectal cancer therapy. Their ultra-small superparamagnetic iron oxide nanoparticles and small interfering RNA appear capable of targeting human vascular endothelial growth factor (VEGF). The rationale underlying their study was to improve the RNA's stability and prolong its retention time in the blood circulation. The system targeted tumor regions, facilitating VEGF silencing and chemotherapy, thus suppressing tumor growth via a multi-dose therapy regimen. The authors also suggest their delivery system acts

as a "negative magnetic resonance imaging contrast agent." The potential application: it could become a powerful tool for diagnosis and for tracking therapeutic outcomes. Future studies will focus on how synergistically combined gene silencing and chemotherapy could be used as a novel colorectal cancer strategy.

Beyond the results achieved so far and the exciting potential suggested by them, studies are also addressing fundamental questions about why nanoparticles are effective in the treatment of cancer. Among these questions are factors that could affect how optimal nanosystems might be engineered. These concerns were addressed by Sykes et al[8] in their report delineating how nanoparticle size, shape, and surface chemistry can affect their accumulation, retention, and penetration in tumors. If more were known about these factors, they suggest, perhaps we could identify certain principles governing the development of optimal nanoparticle technology. Their simulations enabled them to model the process of nanoparticle accumulation. Although too detailed to cover in this article, Sykes et al discovered that changes in pathophysiology associated with tumor volume can selectively change tumor uptake of nanoparticles of varying size. They further report that nanoparticle retention within tumors depends on the frequency of interaction of particles with the perivascular extracellular matrix for smaller nanoparticles. The long-range goal envisioned is that eventually nanoparticles could be personalized based on the patient's disease state in order to achieve optimal outcomes.

One of the consistent concepts in the literature on nanoparticles and cancer describes how enhanced permeability of tumor blood vessels is an important factor. Matsumoto et al[9] explored this concept, reporting that enhanced permeability in tumors is thought to result from malformed vascular walls with leaky cell-to-cell junctions. The authors used an intravital confocal laser scanning microscopy to demonstrate a unique phenomenon: vascular bursts followed by brief vigorous outward flow of fluid that they call eruptions into the tumor interstitial space. As part of the process, "dynamic vents' are thought to form transient opening and closings at these leaky blood vessels. They propose that these eruptions may explain the enhanced extravasation of nanoparticles from the tumor blood vessels. This could also explain how these underlying distribution patterns may enhance the nanoparticle delivery of an administered drug.

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Combining Radiation, Immunotherapy Could Emerge as Exciting New Direction With Potential Mechanisms of Synergy

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If the first efforts are a sign of future progress, one of the next frontiers in the treatment of renal cell carcinoma could include an unlikely source—radiation, traditionally not strongly considered one of the pillars of therapy. Image-guided intensity-modulated radiation therapy, combined with various immunotherapies such as high-dose interleukin-2 and checkpoint inhibitors, could dramatically alter perceptions as part of a new direction—radiosensitizing immunotherapy. The hypothesis: radiation damage induces tumor antigen release and microenvironment changes that could enhance the benefits of immunotherapy.

Preclinical models are building a framework for a potentially exciting new direction in therapy, combining radiotherapy with immunotherapy to enhance the immunogenic response in many cancers, including renal cell carcinoma (RCC). Although the evidence is still preliminary, new information from animal models are pointing toward further exploratory proof-of-concept studies using better immune monitoring to define innovative radiation plus immunotherapy regimens that warrant investigation in larger studies.

Underlying the dynamics of this potential synergistic effect between radiation and immunotherapy are a number of new studies examining response rates to this strategy. Our hypothesis that drove a phase 1 study[1] of stereotactic body radiotherapy (SBRT) and interleukin-2 therapy is that radiation increases tumor antigen release and changes the tumor microenvironment such that the immune effects of IL-2 are significantly more effective in melanoma and RCC. Results from our phase 1 trial were encouraging and a phase 2 study has been launched. The phase 2 randomized trials comparing SBRT and IL-2 vs IL-2 alone will obtain more data about early memory T cell subsets and indirect markers of antigen release and radiation effect such as damage-associated molecular patterns (DAMPs) in relation to response.

There are some intriguing and ironic aspects to this narrative that should not be overlooked, including the fact that radiation has long been considered a generally ineffective strategy in kidney cancer, along with chemotherapy. The evidence for IL-2 effectiveness, however, is long standing, despite its toxicity; this treatment was the first modality to show a curative effect in RCC, albeit modest and generally in the range of 7% or 8%.[2] Our phase 1 study is one of the few reports that show significantly enhanced clinical effects of IL-2 immunotherapy when combined with another agent or modality.[1] Therefore, the results merit interest from another perspective: many investigators have attempted to enhance the efficacy of IL-2 by combining it with chemotherapy, vaccines, cytokines, tumor-infiltrating lymphocyte (TIL) infusions, and monoclonal antibodies.

In view of the results achieved in our phase 1 study, many questions can be asked regarding this approach. For example, what is the mechanism through which SBRT may enhance the response to IL-2? What is the optimal timing of administering SBRT vis-à-vis IL-2? Does SBRT look as promising when combined with other immunotherapies, particularly the checkpoint inhibitors? Is SBRT and IL-2 safe, especially in view of the side effect profile of high-dose IL-2? Recent studies, following the publication of our phase 1 data, are beginning to address these and related questions as they broaden the focus of SBRT and IL-2 to a wider discussion of immunotherapies in general.

For clinicians looking for developments specifically related to RCC management, our phase 1 results are potentially illustrative of how IL-2, long part of the RCC treatment algorithm, could be reinvented with SBRT. The experience with IL-2 is well documented: in metastatic

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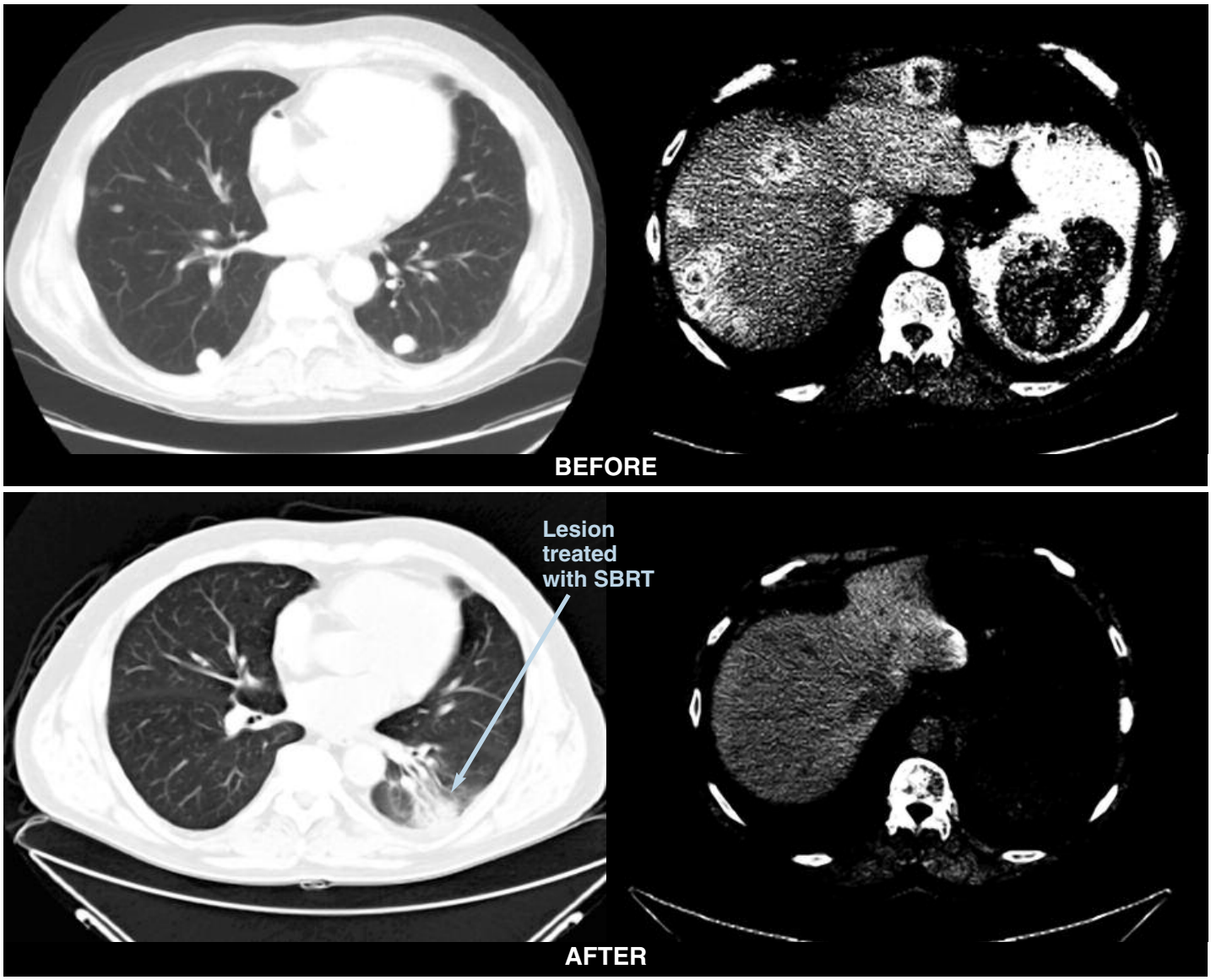

Figure 1. This subject has renal cancer metastatic to lung and liver. The lesion treated with SBRT is indicated. All hepatic and pulmonary metastases regressed and the patient has no FDG-avid lesions on PET imaging now greater than 5 years after therapy. The fibrotic changes in the lung after SBRT are typical.

RCC, the complete response (CR) and partial response (PR) rates are 7% and 8% respectively with a median duration of response of 54 months.[2] More than 70% of patients achieving a CR are alive and disease-free with more than 10 years of follow-up at the last analysis conducted in 2000.[3,4] Efforts to improve selection of RCC patients for high-dose IL-2 therapy have also made significant progress over the last decade, with identification of factors such as CAIX as criteria to determine which patients are more likely to respond to this treatment, although a recent prospective analysis suggested that tumor PD-1 expression may be a more robust biomarker.[5]

The rationale for using SBRT is based on preclinical studies indicating that exposure of tumor cells to high-dose radiation can promote the release of inflammatory cytokines and up-regulate expression of major histocompatibility complex (MHC).[6-11] There is also evidence pointing toward the potential benefit of radiation in possibly mediating an immune response; it appears that tumor cells injured by radiation can release DAMPs or HMGB1. This has been seen to be associated with an immune response.[12] Several other studies also suggest the immune-mediated role of radiation. These authors[13-15] report that high-dose per fraction radiation increases tumor-infiltrating activated CD8+ T cells. The preclinical evidence described by these authors indicates that the T cell response has been associated with enhanced tumor control at distant sites when combined with immunomodulatory agents.

SBRT, IL-2 and Their Effect on Tumor and Immunological Responses

Although it was a relatively small study, our trial reported the response in patients with metastatic melanoma or

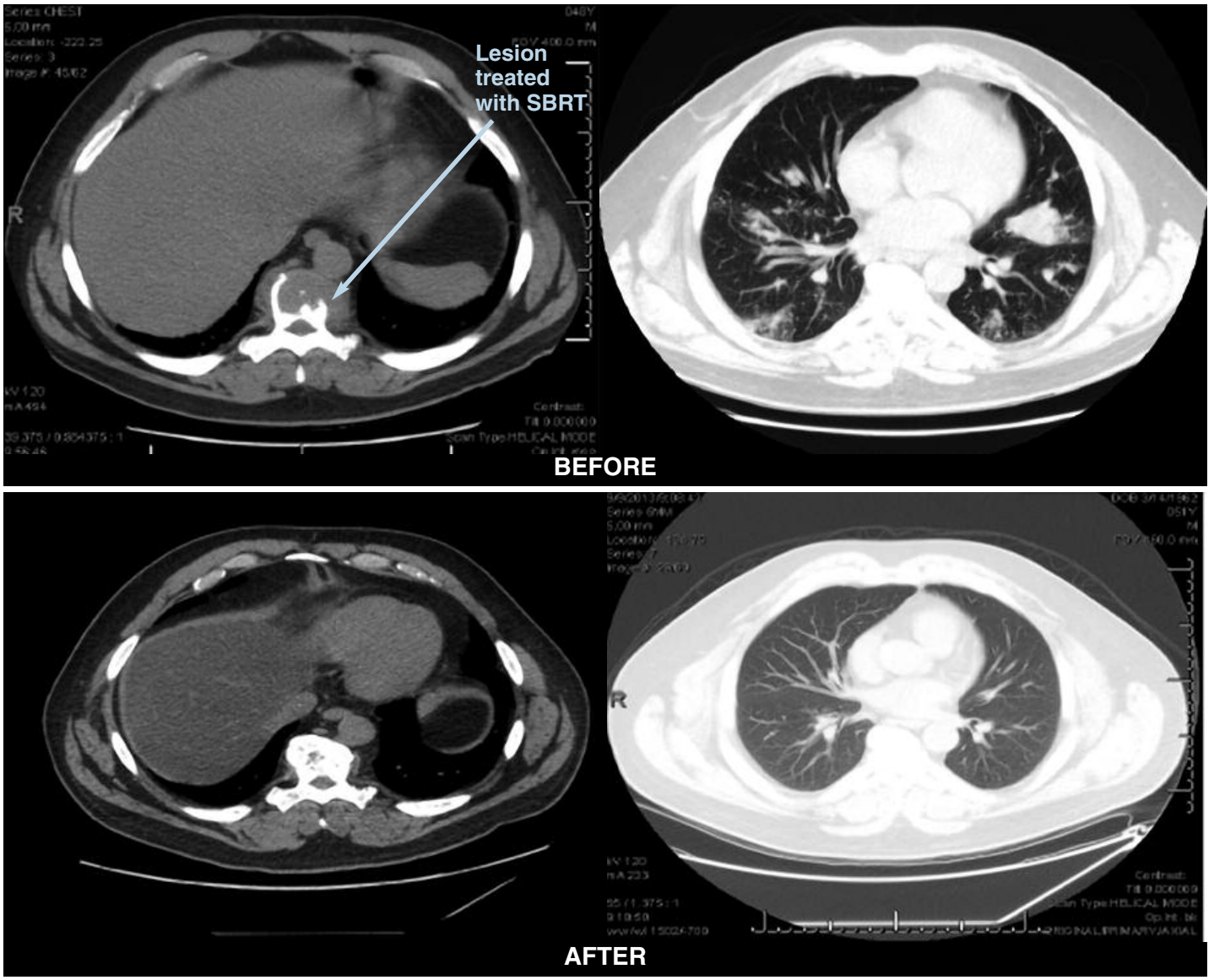

Figure 2. This patient had renal cancer metastatic to bone and lung. The vertebral body metastatic site was treated with SBRT. Multiple pulmonary sites regressed after IL-2 and new bone formation was observed in the skeletal metastatic sites. The patient remains in remission approximately 4 years after completing therapy.

RCC who had not received previous medical therapy for metastatic disease. Patient received one, two or three doses of SBRT (20 Gy per fraction) with the last dose given 3 days before starting IL-2. For IL-2 administration, 600,000 IU per kilogram was given in an IV bolus infusion every 8 hours for a maximum of 14 doses with a second cycle after a 2-week rest. Those who regressed received up to 6 IL-2 cycles.

Among the 12 patients in the intent-to-treat analysis, 11 completed treatment per the study design. Using RECIST criteria, the study assessed overall response in non-irradiated target lesions; 8 of 12 patients had a CR or PR (1 CR and 7 PR); 6 of the patients with PR on CT had a CR by PET imaging. Of those with melanoma, 5 of 7 had a PR or CR and 3 of 5 with RCC had a PR. Immune responses were also measured: responding patients showed a significantly greater frequency of proliferating CD4+T cells with an early activated effector memory phenotype in the peripheral blood. Adverse effects were tolerable and not greater than that anticipated with IL-2 alone, suggesting that the two modalities can be combined safely.

A key point emerging from our study and from other reports is that the dose of radiation is important. Fractionated or high-dose per fraction radiation and not single-dose radiotherapy is the level required to induce the effects seen in our report. Although our sample size was admittedly small, the report is one of the few that show significantly enhanced clinical effects of IL-2 immunotherapy when combined with another agent or modality. One of the issues still needing further study is whether there may be a threshold radiation dose required to enhance immunogenicity. A study by Lee et al, for example, showed that CD8+ T cells exhibited more effective antitumor responses after 20-Gy compared to 5-Gy

radiation fractions.[16] If one considers most of the preclinical studies on this issue, it is evident that the immune enhancing effects of radiation were achieved by using fraction sizes of more than 5 Gy. In our study the objective response of tumors treated with SBRT was 100% compared to 7% in a previous report in which no enhancement of the IL-2 response was observed.[17] Thus, the higher dose fractions and superior tumor targeting may explain the higher overall response rate of SBRT and IL-2 in our study.

As other reports in the literature unravel more of the mechanisms underlying the effectiveness of combining SBRT and immunotherapy, a somewhat clearer understanding of its activity is beginning to emerge. Although our study did not elucidate the mechanism through which SBRT may enhance the response to IL-2, the results suggest that radiation increases tumor antigen release and changes the tumor microenvironment such that the immune effects of IL-2 are significantly more effective in melanoma and perhaps RCC. This hypothesis formed the basis for a new phase 2 randomized clinical trial comparing SBRT and IL-2 vs IL-2 alone in RCC to confirm the response rate and obtain more data about early memory T cell subsets and response. This trial will also include tumor biopsy in selected patients to further determine how the tumor microenvironment could be altered in response to SBRT. Although still preliminary, the thrust of this new trial could break new ground in an approach not envisioned when IL-2 was approved more than 20 years ago for RCC.

As the mechanisms postulated by various reports improve our understanding of the effect of this combined approach on the tumor microenvironment, one area needing more study is the extent to which the immune system is primed by radiation. Should radiosensitization be a prime focus? Our study suggests that it is more a matter of immune system sensitization. In that sense, it is a "radiation event" that can help prime an immune response.

Traditionally, our view of radiation centers around its effect on a local site. However, new concepts introduced by other reports are debunking this notion. For example, a report by Park et al[18] picked up on earlier reports[19-22] that stereotactic ablative radiotherapy (SABR) is increasingly viewed as a noninvasive alternative to surgery. Their report points toward evidence of partial or complete eradication of tumors outside the radiotherapy field, defined as the abscopal effect. It appears that SABR may be able to prime and expand tumor-reactive T cells within the irradiated tumor and in draining lymph nodes. The hypothesis is that these activated, tumor-specific T cells then migrate to and eliminate nonirradiated tumors. This notion seems to be validated in preclinical models establishing that the abscopal effect is T-cell dependent. [23]

The abscopal or systemic effect is receiving more attention and the report by Park et al[18] is a good example of how PD-1 expression may play a role in limiting the effect of radiation on the abscopal effect. PD-1 inhibitors, or checkpoint inhibitors like the recently approved agent, nivolumab for melanoma and RCC, are part of a new effort to enhance the immune system by blocking PD-1 activity. Immune checkpoint blockade at the level of immune priming (CTLA-4 blockade) or effector function (B77-H1/PD-1) is undergoing study in many clinical trials and has shown promising results.

Following up on these concepts, Park et al[18] investigated the influence of PD-1 expression on the systemic antitumor response (abscopal effect) induced by SABR in preclinical melanoma and RCC models. The combination of radiation and PD-1 blockade induced near complete regression of the irradiated primary tumor as opposed to radiation alone or radiation plus control antibody. What's more, the combination of SABR and PD-1 blockade had an effect beyond the localized area. It achieved a 66% reduction in the size of nonirradiated, secondary tumors outside the radiation field or elicited an abscopal effect. The results in this mouse model point toward several conclusions:

- Radiotherapy can elicit and enhance both the priming and effector phases of antitumor T-cell response. As a result, if sufficient effector CD8+ cytotoxic lymphocytes are generated, they can migrate to and infiltrate distant metastatic tumors, at least in this preclinical model.
- Local radiotherapy to the primary tumor is needed to achieve the abscopal effect because anti-PD-1 therapy alone is not effective in suppressing secondary tumors.
- Results from Park et al validate the work of other reports, supporting the concept that local radiotherapy can synergize with checkpoint blockade therapy to promote antitumor immunity.

As checkpoint blockade gets mainstream attention—due to striking and durable clinical responses in some patients with metastatic disease—there is more interest in the biological and mechanistic rationale behind combining radiation with checkpoint blockade immunotherapy. The emphasis of studies so far continues to be on fractionated and not single dose radiotherapy. A case in point is the study by Dewan et al[24] in an animal model that tested the hypothesis that the type of dose-fractionation regimen determines the ability of radiotherapy to synergize with antu-CTLA-4 antibody. The aim of CTLA-4 blockade is to overcome T cell tolerance thereby inhibiting tumor progression.

The report by Dewan et al further substantiates the importance of fractionated radiotherapy. Radiotherapy is usually given in multiple fractions to achieve tumor control while facilitating normal tissue repair within the field (25). With technological advances there is better visualization and targeting of tumors, with selective concentration of dose distributions to achieve a therapeutic advantage.[25] The data from Dewan et al were generated from a mouse model in breast carcinoma. A large single dose of 20 Gy—comparable to what we used in our study—was as effective as the two fractionation regimens

of 8 Gy x 3 and 6 Gy x 5 at controlling the growth of the irradiated tumor. One of the intriguing results from this study concerns a possible "therapeutic window" for the dose of radiation. The regimen of 8 Gy x 3 was superior to 6 Gy x 5 in its ability to induce the abscopal effect and of tumor-specific T cells. Consequently, the window for optimal use of fractionated radiotherapy in this animal model appears to be in this range when used in combination with CTLA-4 blockade. Dewan et al speculate that the clinical use of this strategy may be closer at hand than other studies suggest. When one considers that two CTLA-4 blocking monoclonal antibodies (ipilimumab, approved, and tremelimumab at an advanced stage of testing) could play a role in combination therapy with radiotherapy, the clinical application of these modalities may be in the near future.

As studies continue to build a platform of evidence for radiotherapy as an adjuvant to immunotherapy and encourage the growth of this novel field of radiation oncology,[26] attention has also narrowed to a cluster of ongoing clinical trials described by Crittenden et al. Although these are not targeted to RCC, the ongoing trials initiated nationwide offer insights as to how this field is taking shape. A listing and description of these trials at 7 distinct tumor sites is beyond the scope of this article but they represent initial explorations into what could become a new era of research. They often test the combination of radiotherapy and immunotherapy in a metastatic setting a stage where radiotherapy is traditionally reserved for palliation of symptoms.[26] If the trials can confirm efficacy, perhaps they could facilitate a wider use of these approaches with a therapeutic instead of a palliative intent.

Resolving the Riddle of Recurrence and Resistance

Despite the promising results so far, new studies are already underway to address additional concerns surrounding the combination strategies of radiation and immunotherapy, particularly the use of checkpoint inhibitors. There are fundamental questions of non-redundance and resistance, troublesome issues standing in the way of optimizing responses. The importance of this issue is highlighted by Twyman-Saint Victor et al[27] in melanoma patients and in a mouse model.

Resistance is common among patients receiving checkpoint inhibitors, the authors found that resistance was due to upregulation of PD-L1 on melanoma cells and was associated with T-cell exhaustion. Faced with the quandary of overcoming the resistance due to upregulation of PD-L1, this study looked At PD-L1 blockade as a means of inhibiting resistance and achieving long-term immunity in a murine model. Focusing on the dysfunction in T-cell proliferation and effector function, Twyman-Saint Victor et al found that the addition of anti-PD-L1 improved responses of resistant tumors after radiation and anti-CTLA-4. One of the intriguing results was that for treatment-naïve tumors, responses were even more robust. The addition of a checkpoint inhibitor markedly improved survival and increased complete responses to 80% in the animal model, providing further evidence how, at least on the preclinical level, regimens can be altered to overcome this problem.

Like radiation, surgery is an effective primary therapy in most cancers, resulting in local control and increased duration of survival. In view of the immune suppressive effect of tumors on adaptive immune responses, some authors suggest that surgical removal of the primary tumor has a positive effect on anti-tumor immunity. Similarly, radiation therapy also provides a localized strategy to eliminate the primary tumor. This led Gough et al to propose that there may be similar mechanisms at work with regard to recurrences and immune response among patients who either undergo surgery or radiation. As Gough et al report,[28] in the case of both surgery and radiation, pre-existing microscopic disease beyond the primary tumor can lead to secondary tumors associated with significant mortality. However, recurrence could be mitigated if the tumor-specific adaptive immune response could be enhanced at the time of either radiation therapy or surgery.

In their animal model of sarcoma treatment, surgical removal of 10-14 day established tumors resulted in a 50% rate of local tumor recurrence. With possible implications for the use of radiation and immunotherapy in RCC, Gough et al demonstrated that systemic adjuvant administration of an agonistic antibody directed at OX40, a T-cell co-stimulatory pathway at surgery eliminated local recurrences. T cell co-stimulation through tumor necrosis factor family receptors, like OX40, provides a potent "go" signal that actively promotes the expansion and proliferation of killer CD8 and helper CD4 T cells. Adjuvant use of this agent at the time of surgery eliminated local recurrence in 100% of mice. The authors suggest that a similar strategy could prove effective in combination with radiation, further supporting the role of agonistic antibodies to OX40 in this setting.

Conclusions, Future Directions, Clinical Considerations

Preclinical studies have taken us to the threshold of a potentially new avenue of treatment in RCC. Although the findings are still preliminary, largely exploratory and with few applications as yet, there will be many more reports likely to present more concepts about approaches to combining radiotherapy and immunotherapy.

Dose and fractionation. In their review, Sharabi et al[29] offer key insights and perspective. First, there have been a range of techniques and schedules to deliver radiation therapy in different models, and questions arise as to the optimal strategy. Reports have shown that different time-dose fractionation schedules produce different effects. The consensus so far is that high-dose per fraction radiation (5-20 Gy per fraction) is better than conventionally fractionated schemes of 1.8-2.2 Gy fractions.

Sequencing. Another consensus has emerged on sequencing, at least for now and pending further study and anecdotal reports to the contrary. At this stage, concur-

rent radiation and checkpoint blockade immunotherapy is better than sequential treatments. Radiation before IL-2 appears to be the optimal sequence for this cytokine, which is different than the results for T-cell checkpoint antibodies. There is evidence from Dovedi et al[30] that concurrent checkpoint blockade immunotherapy starting on the day of or during radiation was better than starting such blockade after radiation was completed. Thus, scheduling is an important consideration and deserves to be a focus of future trials to identify a strategy for local and distant disease control.

Special considerations, safety. Among the concerns, as with any combination therapy, is the potential for additive toxicities. Well known contraindications to radiation therapy, such as active scleroderma, must be observed. Clinicians also need to be mindful of the risk of immune-related side effects that may occur at specific sites of irradiation. However, the frequencies of these immune-related side effects associated with checkpoint blockade immunotherapy are fairly well known and management strategies exist, such as withholding or discontinuing checkpoint blockade immunotherapy. Overall, data suggest that radiation can be safely combined with immunotherapy for specific disease sites.

As the established body of work in this field grows, supporting the use of radiation and immunotherapy in RCC, melanoma, and other tumors, there are encouraging signs that these approaches will yield significant advances toward a time when such management becomes part of the treatment algorithm for definitive therapy and curative results.

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SUTENT® (sunitinib malate) IS INDICATED FOR THE TREATMENT OF ADVANCED RENAL CELL CARCINOMA (RCC).

capsules
SUTENT®
sunitinib malate

TAKE ON ADVANCED RCC

IMPORTANT SAFETY INFORMATION

- **Hepatotoxicity has been observed in clinical trials and post-marketing experience. This hepatotoxicity may be severe, and deaths have been reported.** Monitor liver function tests before initiation of treatment, during each cycle of treatment, and as clinically indicated. SUTENT should be interrupted for Grade 3 or 4 drug-related hepatic adverse events and discontinued if there is no resolution. Do not restart SUTENT if patients subsequently experience severe changes in liver function tests or have other signs and symptoms of liver failure
- **Women of childbearing potential** should be advised of the potential hazard to the fetus and to avoid becoming pregnant
- Given the potential for serious adverse reactions (ARs) in **nursing infants,** a decision should be made whether to discontinue nursing or SUTENT

Please see additional Important Safety Information and Brief Summary, including BOXED WARNING, on the following pages.

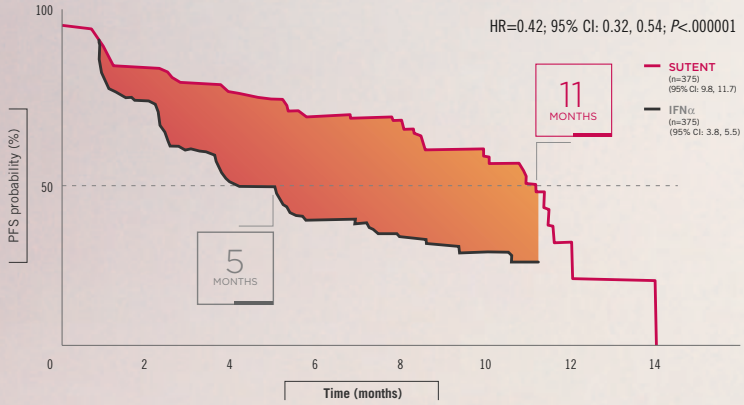
SUTENT® (sunitinib malate) IS INDICATED FOR THE TREATMENT OF ADVANCED RENAL CELL CARCINOMA (RCC).

DESIGNED FOR EFFICACY. ADJUSTABLE WHEN NEEDED.

SUTENT delivers proven efficacy. Dose adjustments may be made based on patient tolerability.

In the phase 3 trial, which allowed dose modifications, SUTENT demonstrated 11 months' median PFS in 1st-line mRCC

PRIMARY ENDPOINT



- **54%** of patients on SUTENT had **dose interruptions** and **52%** had **dose reductions** (vs 39% and 27% with IFNα, respectively)

Results are from the large (N=750), phase 3, randomized, multicenter trial comparing SUTENT with IFNα in patients with treatment-naïve mRCC. Primary endpoint was progression-free survival (PFS). Secondary endpoints included objective response rate (ORR), overall survival (OS), and safety.

- Patients were randomized to receive either 50-mg SUTENT once daily in cycles of 4 weeks on/2 weeks off (Schedule 4/2), or 9 MIU IFNα 3 times per week until disease progression or study withdrawal

IMPORTANT SAFETY INFORMATION (cont'd)

- **Cardiovascular events,** including heart failure, cardiomyopathy, myocardial ischemia, and myocardial infarction, some of which were fatal, have been reported. Use SUTENT with caution in patients who are at risk for, or who have a history of, these events. Monitor patients for signs and symptoms of congestive heart failure (CHF) and, in the presence of clinical manifestations, discontinuation is recommended. Patients who presented with cardiac events, pulmonary embolism, or cerebrovascular events within the previous 12 months were excluded from clinical studies
- SUTENT has been shown to **prolong QT interval** in a dose-dependent manner, which may lead to an increased risk for ventricular arrhythmias including **Torsades de Pointes,** which has been seen in <0.1% of patients. Monitoring with on-treatment electrocardiograms and electrolytes should be considered
- **Hypertension** may occur. Monitor blood pressure and treat as needed with standard antihypertensive therapy. In cases of severe hypertension, temporary suspension of SUTENT is recommended until hypertension is controlled
- There have been (<1%) reports, some fatal, of subjects presenting with seizures and radiological evidence of **reversible posterior leukoencephalopathy syndrome (RPLS)**
- **Hemorrhagic events,** including tumor-related hemorrhage such as pulmonary hemorrhage, have occurred. Some of these events were fatal. Perform serial complete blood counts (CBCs) and physical examinations
- Cases of **tumor lysis syndrome (TLS)** have been reported primarily in patients with high tumor burden. Monitor these patients closely and treat as clinically indicated
- **Thrombotic microangiopathy (TMA),** including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome, sometimes leading to renal failure or a fatal outcome, has been reported in patients who received SUTENT as monotherapy and in combination with bevacizumab. Discontinue SUTENT in patients developing TMA. Reversal of the effects of TMA has been observed after treatment was discontinued
- **Proteinuria** and nephrotic syndrome have been reported. Some of these cases have resulted in renal failure and fatal outcomes. Perform baseline and periodic urinalysis during treatment, with follow-up measurement of 24-hour urine protein as clinically indicated. Interrupt SUTENT and dose-reduce if 24-hour urine protein is ≥3 g; discontinue SUTENT in cases of nephrotic syndrome or repeat episodes of urine protein ≥3 g despite dose reductions

SUTENT® capsules
sunitinib malate

A well-known adverse reaction (AR) profile

In the phase 3, randomized, 1st-line mRCC trial vs IFNα (N=750)

THE MOST COMMON ARs occurring in ≥20% of patients receiving SUTENT for treatment-naïve metastatic RCC (all grades, vs IFNα)

Diarrhea (66% vs 21%), fatigue (62% vs 56%), nausea (58% vs 41%), anorexia (48% vs 42%), altered taste (47% vs 15%), mucositis/stomatitis (47% vs 5%), pain in extremity/limb discomfort (40% vs 30%), vomiting (39% vs 17%), bleeding, all sites (37% vs 10%), hypertension (34% vs 4%), dyspepsia (34% vs 4%), arthralgia (30% vs 19%), abdominal pain (30% vs 12%), rash (29% vs 11%), hand-foot syndrome (29% vs 1%), back pain (28% vs 14%), cough (27% vs 14%), asthenia (26% vs 22%), dyspnea (26% vs 20%), skin discoloration/yellow skin (25% vs 0%), peripheral edema (24% vs 5%), headache (23% vs 19%), constipation (23% vs 14%), dry skin (23% vs 7%), fever (22% vs 37%), and hair color changes (20% vs <1%)

THE MOST COMMON GRADE 3/4 ARs (occurring in ≥5% of patients with RCC receiving SUTENT vs IFNα)

Fatigue (15% vs 15%), hypertension (13% vs <1%), asthenia (11% vs 6%), diarrhea (10% vs <1%), hand-foot syndrome (8% vs 0%), dyspnea (6% vs 4%), nausea (6% vs 2%), back pain (5% vs 2%), pain in extremity/limb discomfort (5% vs 2%), vomiting (5% vs 1%), and abdominal pain (5% vs 1%)

THE MOST COMMON GRADE 3/4 LAB ABNORMALITIES (occurring in ≥5% of patients with RCC receiving SUTENT vs IFNα)

Lymphocytes (18% vs 26%), lipase (18% vs 8%), neutrophils (17% vs 9%), uric acid (14% vs 8%), platelets (9% vs 1%), hemoglobin (8% vs 5%), sodium decreased (8% vs 4%), leukocytes (8% vs 2%), glucose increased (6% vs 6%), phosphorus (6% vs 6%), and amylase (6% vs 3%)

Dosing overview

WEEK 1	WEEK 2	WEEK 3	WEEK 4	WEEK 5	WEEK 6
on	on	on	on	off	off

Recommended dose for advanced RCC is one 50-mg capsule taken orally once daily, on a schedule of 4 weeks on treatment followed by 2 weeks off

- Dose modification and/or dose interruption is recommended based on individual patient safety and tolerability
- SUTENT may be taken with or without food
- Remind patients to disclose any prescription or nonprescription medications they are taking, including bisphosphonates, vitamins, and herbal supplements, which can interact with SUTENT in different ways

When tolerability is a concern...

Dose modification per FDA label

For illustrative purposes only.

- The dose of SUTENT may be adjusted in 12.5-mg increments or decrements, based on individual patient safety and tolerability
- Dose adjustments are recommended when SUTENT is administered with CYP3A4 inhibitors or inducers. During treatment with SUTENT, patients should not drink grapefruit juice, eat grapefruit, or take St John's Wort
- No dose adjustment is recommended based on age, race, gender, body weight, creatinine clearance, ECOG performance status score, or hepatic impairment (Child-Pugh Class A or B)

Dose interruption considerations from retrospective studies

WEEK 1	WEEK 2	WEEK 3
on	on	off

- In patients with advanced RCC who are unable to tolerate Schedule 4/2, consider the dose reduction described in the FDA-approved label or, as an alternative, consider modifying the schedule to 2 weeks on treatment followed by 1 week off (Schedule 2/1) using the same dose
  - —Studies supporting Schedule 2/1 have not been reviewed by the FDA. For most studies, the patient population was small and/or analysis was post hoc, and therefore susceptible to bias. The efficacy of any particular alternative dosing schedule has not been established[1-5]

IMPORTANT SAFETY INFORMATION (cont'd)

- **Severe cutaneous reactions** have been reported, including cases of erythema multiforme (EM), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), some of which were fatal. If signs or symptoms of EM, SJS, or TEN are present, SUTENT treatment should be discontinued. If a diagnosis of SJS or TEN is suspected, treatment must not be re-started. Necrotizing fasciitis, including fatal cases, has been reported, including of the perineum and secondary to fistula formation. Discontinue SUTENT in patients who develop necrotizing fasciitis
- **Thyroid dysfunction** may occur. Monitor thyroid function in patients with signs and/or symptoms of thyroid dysfunction, including hypothyroidism, hyperthyroidism, and thyroiditis, and treat per standard medical practice
- SUTENT has been associated with symptomatic **hypoglycemia,** which may result in loss of consciousness or require hospitalization. Reductions in blood glucose levels may be worse in patients with diabetes. Check blood glucose levels regularly during and after discontinuation of SUTENT. Assess whether antidiabetic drug dosage needs to be adjusted to minimize the risk of hypoglycemia
- **Osteonecrosis of the jaw (ONJ)** has been reported. Consider preventive dentistry prior to treatment with SUTENT. If possible, avoid invasive dental procedures, particularly in patients receiving bisphosphonates
- Cases of **impaired wound healing** have been reported. Temporary interruption of therapy with SUTENT is recommended in patients undergoing major surgical procedures
- **Adrenal hemorrhage** was observed in animal studies. Monitor adrenal function in case of stress such as surgery, trauma, or severe infection
- **CBCs** with platelet count and serum chemistries including phosphate should be performed at the beginning of each treatment cycle for patients receiving treatment with SUTENT
- Dose adjustments are recommended when SUTENT is administered with **CYP3A4 inhibitors or inducers.** During treatment with SUTENT, patients should not drink grapefruit juice, eat grapefruit, or take St John's Wort

Please see Brief Summary, including BOXED WARNING, on the following pages.

February 2016

Pfizer U.S. Pharmaceuticals

References: 1. Atkinson BJ, Kalra S, Wang X, et al. Clinical outcomes for patients with metastatic renal cell carcinoma treated with alternative sunitinib schedules. *J Urol*. 2014;191(3):611-618. **2.** Bjarnason GA, Khalil B, Hudson JM, et al. Outcomes in patients with metastatic renal cell cancer treated with individualized sunitinib therapy: correlation with dynamic microbubble ultrasound data and review of the literature. *Urol Oncol*. 2014;32(4):480-487. **3.** Kondo T, Takagi T, Kobayashi H, et al. Superior tolerability of altered dosing schedule of sunitinib with 2-weeks-on and 1-week-off in patients with metastatic renal cell carcinoma—comparison to standard dosing schedule of 4-weeks-on and 2-weeks-off. *Jpn J Clin Oncol*. 2014;44(3):270-277. **4.** Najjar YG, Mittal K, Elson P, et al. A 2 weeks on and 1 week off schedule of sunitinib is associated with decreased toxicity in metastatic renal cell carcinoma. *Eur J Cancer*. 2014;50(6):1084-1089. **5.** Bracarda S, Iacovelli R, Boni L, et al. Sunitinib administered on 2/1 schedule in patients with metastatic renal cell carcinoma: the RAINBOW analysis. *Ann Oncol*. 2015;26(10):2107-2113.

SUTENT® (SUNITINIB MALATE) CAPSULES, ORAL

Brief Summary of Prescribing Information

WARNING: HEPATOTOXICITY
Hepatotoxicity has been observed in clinical trials and post-marketing experience. This hepatotoxicity may be severe, and deaths have been reported. *[See Warnings and Precautions]*

INDICATION AND USAGE: SUTENT is indicated for the treatment of advanced renal cell carcinoma (RCC).

DOSAGE AND ADMINISTRATION

Recommended Dose. The recommended dose of SUTENT for advanced RCC is one 50 mg oral dose taken once daily, on a schedule of 4 weeks on treatment followed by 2 weeks off (Schedule 4/2). SUTENT may be taken with or without food.

Dose Modification. Dose interruption and/or dose modification in 12.5 mg increments or decrements is recommended based on individual safety and tolerability.

A dose reduction for SUTENT to a minimum of 37.5 mg daily should be considered if SUTENT must be co-administered with a strong CYP3A4 inhibitor.

A dose increase for SUTENT to a maximum of 87.5 mg daily should be considered if SUTENT must be co-administered with a CYP3A4 inducer. If dose is increased, the patient should be monitored carefully for toxicity.

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS

Hepatotoxicity. SUTENT has been associated with hepatotoxicity, which may result in liver failure or death. Liver failure has been observed in clinical trials (7/2281 [0.3%]) and post-marketing experience. Liver failure signs include jaundice, elevated transaminases and/or hyperbilirubinemia in conjunction with encephalopathy, coagulopathy, and/or renal failure. Monitor liver function tests (ALT, AST, bilirubin) before initiation of treatment, during each cycle of treatment, and as clinically indicated. SUTENT should be interrupted for Grade 3 or 4 drug-related hepatic adverse events and discontinued if there is no resolution. Do not restart SUTENT if patients subsequently experience severe changes in liver function tests or have other signs and symptoms of liver failure.

Safety in patients with ALT or AST >2.5 x ULN or, if due to liver metastases, >5.0 x ULN has not been established.

Pregnancy. SUTENT can cause fetal harm when administered to a pregnant woman. As angiogenesis is a critical component of embryonic and fetal development, inhibition of angiogenesis following administration of SUTENT should be expected to result in adverse effects on pregnancy. In animal reproductive studies in rats and rabbits, sunitinib was teratogenic, embryotoxic, and fetotoxic. There are no adequate and well-controlled studies of SUTENT in pregnant women. If the drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with SUTENT.

Cardiovascular Events. In the presence of clinical manifestations of congestive heart failure (CHF), discontinuation of SUTENT is recommended. The dose of SUTENT should be interrupted and/or reduced in patients without clinical evidence of CHF but with an ejection fraction <50% and >20% below baseline. Cardiovascular events, including heart failure, cardiomyopathy, myocardial ischemia, and myocardial infarction, some of which were fatal, have been reported. Use SUTENT with caution in patients who are at risk for, or who have a history of, these events. More patients treated with SUTENT experienced decline in left ventricular ejection fraction (LVEF) than patients receiving interferon-α (IFN-α).

In the treatment-naïve RCC study, 103/375 (27%) and 54/360 (15%) patients on SUTENT and IFN-α, respectively, had an LVEF value below the LLN. Twenty-six patients on SUTENT (7%) and seven on IFN-α (2%) experienced declines in LVEF to >20% below baseline and to below 50%. Left ventricular dysfunction was reported in four patients (1%) and CHF in two patients (<1%) who received SUTENT.

Patients who presented with cardiac events within 12 months prior to SUTENT administration, such as myocardial infarction (including severe/unstable angina), coronary/peripheral artery bypass graft, symptomatic CHF, cerebrovascular accident or transient ischemic attack, or pulmonary embolism were excluded from SUTENT clinical studies. It is unknown whether patients with these concomitant conditions may be at a higher risk of developing drug-related left ventricular dysfunction. Physicians are advised to weigh this risk against the potential benefits of the drug. **These patients should be carefully monitored for clinical signs and symptoms of CHF while receiving SUTENT. Baseline and periodic evaluations of LVEF should also be considered while these patients are receiving SUTENT. In patients without cardiac risk factors, a baseline evaluation of ejection fraction should be considered.**

QT Interval Prolongation and Torsade de Pointes. SUTENT has been shown to prolong the QT interval in a dose dependent manner, which may lead to an increased risk for ventricular arrhythmias including Torsade de Pointes. Torsade de Pointes has been observed in <0.1% of SUTENT-exposed patients.

SUTENT should be used with caution in patients with a history of QT interval prolongation, patients who are taking antiarrhythmics, or patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances. When using SUTENT, periodic monitoring with on-treatment electrocardiograms and electrolytes (magnesium, potassium) should be considered. Concomitant treatment with strong CYP3A4 inhibitors, which may increase sunitinib plasma concentrations, should be used with caution and dose reduction of SUTENT should be considered *[see Dosage and Administration]*.

Hypertension. Patients should be monitored for hypertension and treated as needed with standard anti-hypertensive therapy. In cases of severe hypertension, temporary suspension of SUTENT is recommended until hypertension is controlled.

Of patients receiving SUTENT for treatment-naïve RCC, 127/375 patients (34%) receiving SUTENT compared with 13/360 patients (4%) on IFN-α experienced hypertension. Grade 3 hypertension was observed in 50/375 treatment-naïve RCC patients (13%) on SUTENT compared to 1/360 patients (<1%) on IFN-α. No Grade 4 hypertension was reported. SUTENT dosing was reduced or temporarily delayed for hypertension in 21/375 patients (6%) on the treatment-naïve RCC study. Four treatment-naïve RCC patients, including one with malignant hypertension, discontinued treatment due to hypertension. Severe hypertension (>200 mmHg systolic or 110 mmHg diastolic) occurred in 32/375 treatment-naïve RCC patients (9%) on SUTENT and 3/360 patients (1%) on IFN-α.

Hemorrhagic Events. Hemorrhagic events reported through post-marketing experience, some of which were fatal, have included GI, respiratory, tumor, urinary tract and brain hemorrhages. In patients receiving SUTENT in a clinical trial for treatment-naïve RCC, 140/375 patients (37%) had bleeding events compared with 35/360 patients (10%) receiving IFN-α. Epistaxis was the most common hemorrhagic adverse event reported. Less common bleeding events included rectal, gingival, upper gastrointestinal, genital, and wound bleeding. Most events in RCC patients were Grade 1 or 2; there was one Grade 5 event of gastric bleed in a treatment-naïve patient.

Tumor-related hemorrhage has been observed in patients treated with SUTENT. These events may occur suddenly, and in the case of pulmonary tumors may present as severe and life-threatening hemoptysis or pulmonary hemorrhage. Cases of pulmonary hemorrhage, some with a fatal outcome, have been observed in clinical trials and have been reported in post-marketing experience in patients treated with SUTENT. Clinical assessment of these events should include serial complete blood counts (CBCs) and physical examinations.

Serious, sometimes fatal gastrointestinal complications including gastrointestinal perforation, have occurred rarely in patients with intra-abdominal malignancies treated with SUTENT.

Tumor Lysis Syndrome (TLS). Cases of TLS, some fatal, have occurred in patients treated with SUTENT. Patients generally at risk of TLS are those with high tumor burden prior to treatment. These patients should be monitored closely and treated as clinically indicated.

Thrombotic Microangiopathy. Thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome, sometimes leading to renal failure or a fatal outcome, has been reported in clinical trials and in post-marketing experience of SUTENT as monotherapy and in combination with bevacizumab. Discontinue SUTENT in patients developing TMA. Reversal of the effects of TMA has been observed after treatment was discontinued.

Proteinuria. Proteinuria and nephrotic syndrome have been reported. Some of these cases have resulted in renal failure and fatal outcomes. Monitor patients for the development or worsening of proteinuria. Perform baseline and periodic urinalyses during treatment, with follow up measurement of 24-hour urine protein as clinically indicated. Interrupt SUTENT and dose reduce for 24-hour urine protein ≥ 3 grams. Discontinue SUTENT for patients with nephrotic syndrome or repeat episodes of urine protein ≥ 3 grams despite dose reductions. The safety of continued SUTENT treatment in patients with moderate to severe proteinuria has not been systematically evaluated.

Dermatologic Toxicities. Severe cutaneous reactions have been reported, including cases of erythema multiforme (EM), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), some of which were fatal. If signs or symptoms of SJS, TEN, or EM (e.g., progressive skin rash often with blisters or mucosal lesions) are present, SUTENT treatment should be discontinued. If a diagnosis of SJS or TEN is suspected, SUTENT treatment must not be re-started.

Necrotizing fasciitis, including fatal cases, has been reported in patients treated with SUTENT, including of the perineum and secondary to fistula formation. Discontinue SUTENT in patients who develop necrotizing fasciitis.

Thyroid Dysfunction. Baseline laboratory measurement of thyroid function is recommended and patients with hypothyroidism or hyperthyroidism should be treated as per standard medical practice prior to the start of SUTENT treatment. All patients should be observed closely for signs and symptoms of thyroid dysfunction, including hypothyroidism, hyperthyroidism, and thyroiditis, on SUTENT treatment. Patients with signs and/or symptoms suggestive of thyroid dysfunction should have laboratory monitoring of thyroid function performed and be treated as per standard medical practice.

Hypothyroidism was reported as an adverse reaction in sixty-one patients (16%) on SUTENT in the treatment-naïve RCC study and in three patients (1%) in the IFN-α arm.

Cases of hyperthyroidism, some followed by hypothyroidism, have been reported in clinical trials and through post-marketing experience.

Hypoglycemia. SUTENT has been associated with symptomatic hypoglycemia, which may result in loss of consciousness, or require hospitalization. Hypoglycemia has occurred in clinical trials in 2% of the patients treated with SUTENT for RCC. Reductions in blood glucose levels may be worse in diabetic patients. Check blood glucose levels regularly during and after discontinuation of treatment with SUTENT. Assess if anti-diabetic drug dosage needs to be adjusted to minimize the risk of hypoglycemia.

Osteonecrosis of the Jaw (ONJ). ONJ has been observed in clinical trials and has been reported in post-marketing experience in patients treated with SUTENT. Concomitant exposure to other risk factors, such as bisphosphonates or dental disease, may increase the risk of osteonecrosis of the jaw.

Wound Healing. Cases of impaired wound healing have been reported during SUTENT therapy. Temporary interruption of SUTENT therapy is recommended for precautionary reasons in patients undergoing major surgical procedures. There is limited clinical experience regarding the timing of reinitiation of therapy following major surgical intervention. Therefore, the decision to resume SUTENT therapy following a major surgical intervention should be based upon clinical judgment of recovery from surgery.

Adrenal Function. Physicians prescribing SUTENT are advised to monitor for adrenal insufficiency in patients who experience stress such as surgery, trauma or severe infection.

Adrenal toxicity was noted in non-clinical repeat dose studies of 14 days to 9 months in rats and monkeys at plasma exposures as low as 0.7 times the AUC observed in clinical studies. Histological changes of the adrenal gland were characterized as hemorrhage, necrosis, congestion, hypertrophy and inflammation. In clinical studies, CT/MRI obtained in 336 patients after exposure to one or more cycles of SUTENT demonstrated no evidence of adrenal hemorrhage or necrosis. ACTH stimulation testing was performed in approximately 400 patients across multiple clinical trials of SUTENT. Among patients with normal baseline ACTH stimulation testing, one patient developed consistently abnormal test results during treatment that are unexplained and may be related to treatment with SUTENT. Eleven additional patients with normal baseline testing had abnormalities in the final test performed, with peak cortisol levels of 12-16.4 mcg/dL (normal >18 mcg/dL) following stimulation.
None of these patients were reported to have clinical evidence of adrenal insufficiency.

Laboratory Tests. CBCs with platelet count and serum chemistries including phosphate should be performed at the beginning of each treatment cycle for patients receiving treatment with SUTENT.

ADVERSE REACTIONS

The data described below reflect exposure to SUTENT in 660 patients who participated in the double-blind treatment phase of a placebo-controlled trial (n=202) for the treatment of gastrointestinal stromal tumor (GIST), an active-controlled trial (n=375) for the treatment of RCC or a placebo-controlled trial (n=83) for the treatment of pancreatic neuroendocrine tumors (pNET). The RCC patients received a starting oral dose of 50 mg daily on Schedule 4/2 in repeated cycles.

The most common adverse reactions (≥20%) in patients with GIST, RCC or pNET are fatigue, asthenia, fever, diarrhea, nausea, mucositis/stomatitis, vomiting, dyspepsia, abdominal pain, constipation, hypertension, peripheral edema, rash, hand-foot syndrome, skin discoloration, dry skin, hair color changes, altered taste, headache, back pain, arthralgia, extremity pain, cough, dyspnea, anorexia, and bleeding. The potentially serious adverse reactions of hepatotoxicity, left ventricular dysfunction, QT interval prolongation, hemorrhage, hypertension, thyroid dysfunction, and adrenal function are discussed in *Warnings and Precautions*. Other adverse reactions occurring in RCC studies are described below.

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

Adverse Reactions in the Treatment-Naïve RCC Study. The as-treated patient population for the treatment-naïve RCC study included 735 patients, 375 randomized to SUTENT and 360 randomized to IFN-α. The median duration of treatment was 11.1 months (range: 0.4 - 46.1) for SUTENT treatment and 4.1 months (range: 0.1 - 45.6) for IFN-α treatment. Dose interruptions occurred in 202 patients (54%) on SUTENT and 141 patients (39%) on IFN-α. Dose reductions occurred in 194 patients (52%) on SUTENT and 98 patients (27%) on IFN-α. Discontinuation rates due to adverse reactions were 20% for SUTENT and 24% for IFN-α. Most treatment-emergent adverse reactions in both study arms were Grade 1 or 2 in severity. Grade 3 or 4 treatment-emergent adverse reactions were reported in 77% versus 55% of patients on SUTENT versus IFN-α, respectively.

The following table compares the incidence of common (≥10%) treatment-emergent adverse reactions for patients receiving SUTENT versus IFN-α.

Adverse Reactions Reported in at Least 10% of Patients with RCC Who Received SUTENT or IFN-α*

	SUTENT (n=375)		IFN-α (n=360)	
Adverse Reaction, n (%)	**All Grades**	**Grade 3/4[a]**	**All Grades**	**Grade 3/4[b]**
Any	372 (99)	290 (77)	355 (99)	197 (55)
Constitutional				
Fatigue	233 (62)	55 (15)	202 (56)	54 (15)
Asthenia	96 (26)	42 (11)	81 (22)	21 (6)
Fever	84 (22)	3 (1)	134 (37)	1 (<1)
Weight decreased	60 (16)	1 (<1)	60 (17)	3 (1)
Chills	53 (14)	3 (1)	111 (31)	0 (0)
Chest Pain	50 (13)	7 (2)	24 (7)	3 (1)
Influenza like illness	18 (5)	0 (0)	54 (15)	1 (<1)
Gastrointestinal				
Diarrhea	246 (66)	37 (10)	76 (21)	1 (<1)
Nausea	216 (58)	21 (6)	147 (41)	6 (2)
Mucositis/stomatitis	178 (47)	13 (3)	19 (5)	2 (<1)
Vomiting	148 (39)	19 (5)	62 (17)	4 (1)
Dyspepsia	128 (34)	8 (2)	16 (4)	0 (0)
Abdominal pain[c]	113 (30)	20 (5)	42 (12)	5 (1)
Constipation	85 (23)	4 (1)	49 (14)	1 (<1)
Dry mouth	50 (13)	0 (0)	27 (7)	1 (<1)
GERD/reflux esophagitis	47 (12)	1 (<1)	3 (1)	0 (0)
Flatulence	52 (14)	0 (0)	8 (2)	0 (0)
Oral pain	54 (14)	2 (<1)	2 (1)	0 (0)
Glossodynia	40 (11)	0 (0)	2 (1)	0 (0)
Hemorrhoids	38 (10)	0 (0)	6 (2)	0 (0)
Cardiac				
Hypertension	127 (34)	50 (13)	13 (4)	1 (<1)
Edema, peripheral	91 (24)	7 (2)	17 (5)	2 (1)
Ejection fraction decreased	61 (16)	10 (3)	19 (5)	6 (2)

Adverse Reactions Reported in at Least 10% of Patients with RCC Who Received SUTENT or IFN-α* (cont'd)

Adverse Reaction, n (%)	SUTENT (n=375)		IFN-α (n=360)	
	All Grades	Grade 3/4[a]	All Grades	Grade 3/4[b]
Dermatology				
Rash	109 (29)	6 (2)	39 (11)	1 (<1)
Hand-foot syndrome	108 (29)	32 (8)	3 (1)	0 (0)
Skin discoloration/ yellow skin	94 (25)	1 (<1)	0 (0)	0 (0)
Dry skin	85 (23)	1 (<1)	26 (7)	0 (0)
Hair color changes	75 (20)	0 (0)	1 (<1)	0 (0)
Pruritus	44 (12)	1 (<1)	24 (7)	1 (<1)
Neurology				
Altered taste[d]	178 (47)	1 (<1)	54 (15)	0 (0)
Headache	86 (23)	4 (1)	69 (19)	0 (0)
Dizziness	43 (11)	2 (<1)	50 (14)	2 (1)
Musculoskeletal				
Back pain	105 (28)	19 (5)	52 (14)	7 (2)
Arthralgia	111 (30)	10 (3)	69 (19)	4 (1)
Pain in extremity/ limb discomfort	150 (40)	19 (5)	107 (30)	7 (2)
Endocrine				
Hypothyroidism	61 (16)	6 (2)	3 (1)	0 (0)
Respiratory				
Cough	100 (27)	3 (1)	51 (14)	1 (<1)
Dyspnea	99 (26)	24 (6)	71 (20)	15 (4)
Nasopharyngitis	54 (14)	0 (0)	8 (2)	0 (0)
Oropharyngeal Pain	51 (14)	2 (<1)	9 (2)	0 (0)
Upper respiratory tract infection	43 (11)	2 (<1)	9 (2)	0 (0)
Metabolism/Nutrition				
Anorexia[e]	182 (48)	11 (3)	153 (42)	7 (2)
Hemorrhage/Bleeding				
Bleeding, all sites	140 (37)	16 (4)[f]	35 (10)	3 (1)
Psychiatric				
Insomnia	57 (15)	3 (<1)	37 (10)	0 (0)
Depression[g]	40 (11)	0 (0)	51 (14)	5 (1)

*Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0
[a]Grade 4 ARs in patients on SUTENT included back pain (1%), arthralgia (<1%), dyspnea (<1%), asthenia (<1%), fatigue (<1%), limb pain (<1%) and rash (<1%).
[b]Grade 4 ARs in patients on IFN-α included dyspnea (1%), fatigue (1%), abdominal pain (<1%) and depression (<1%).
[c]Includes flank pain
[d]Includes ageusia, hypogeusia and dysgeusia
[e]Includes decreased appetite
[f]Includes one patient with Grade 5 gastric hemorrhage
[g]Includes depressed mood

Treatment-emergent Grade 3/4 laboratory abnormalities are presented below.

Laboratory Abnormalities Reported in at Least 10% of Treatment-Naïve RCC Patients Who Received SUTENT or IFN-α

Laboratory Parameter, n (%)	SUTENT (n=375)		IFN-α (n=360)	
	All Grades*	Grade 3/4*[a]	All Grades*	Grade 3/4*[b]
Gastrointestinal				
AST	211 (56)	6 (2)	136 (38)	8 (2)
ALT	192 (51)	10 (3)	144 (40)	9 (2)
Lipase	211 (56)	69 (18)	165 (46)	29 (8)
Alkaline phosphatase	171 (46)	7 (2)	132 (37)	6 (2)
Amylase	130 (35)	22 (6)	114 (32)	12 (3)
Total bilirubin	75 (20)	3 (1)	8 (2)	0 (0)
Indirect bilirubin	49 (13)	4 (1)	3 (1)	0 (0)
Renal/Metabolic				
Creatinine	262 (70)	2 (<1)	183 (51)	1 (<1)
Creatine kinase	183 (49)	9 (2)	40 (11)	4 (1)
Uric acid	173 (46)	54 (14)	119 (33)	29 (8)
Calcium decreased	156 (42)	4 (1)	145 (40)	4 (1)
Phosphorus	116 (31)	22 (6)	87 (24)	23 (6)
Albumin	106 (28)	4 (1)	72 (20)	0 (0)
Glucose increased	86 (23)	21 (6)	55 (15)	22 (6)
Sodium decreased	75 (20)	31 (8)	55 (15)	13 (4)
Glucose decreased	65 (17)	0 (0)	43 (12)	1 (<1)
Potassium increased	61 (16)	13 (3)	61 (17)	15 (4)
Calcium increased	50 (13)	2 (<1)	35 (10)	5 (1)
Potassium decreased	49 (13)	3 (1)	7 (2)	1 (<1)
Sodium increased	48 (13)	0 (0)	38 (10)	0 (0)
Hematology				
Neutrophils	289 (77)	65 (17)	178 (49)	31 (9)
Hemoglobin	298 (79)	29 (8)	250 (69)	18 (5)
Platelets	255 (68)	35 (9)	85 (24)	2 (1)
Lymphocytes	256 (68)	66 (18)	245 (68)	93 (26)
Leukocytes	293 (78)	29 (8)	202 (56)	8 (2)

*Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0
[a]Grade 4 laboratory abnormalities in patients on SUTENT included uric acid (14%), lipase (3%), neutrophils (2%), lymphocytes (2%), hemoglobin (2%), platelets (1%), amylase (1%), ALT (<1%), creatine kinase (<1%), creatinine (<1%), glucose increased (<1%), calcium decreased (<1%), phosphorous (<1%), potassium increased (<1%), and sodium decreased (<1%).
[b]Grade 4 laboratory abnormalities in patients on IFN-α included uric acid (8%), lymphocytes (2%), lipase (1%), neutrophils (1%), amylase (<1%), calcium increased (<1%), glucose decreased (<1%), potassium increased (<1%) and hemoglobin (<1%).

Venous Thromboembolic Events. Thirteen (3%) patients receiving SUTENT for treatment-naïve RCC had venous thromboembolic events reported. Seven (2%) of these patients had pulmonary embolism, one was Grade 2 and six were Grade 4, and six (2%) patients had DVT, including three Grade 3. One patient was permanently withdrawn from SUTENT due to pulmonary embolism; dose interruption occurred in two patients with pulmonary embolism and one with DVT. In treatment-naïve RCC patients receiving IFN-α, six (2%) venous thromboembolic events occurred; one patient (<1%) experienced a Grade 3 DVT and five patients (1%) had pulmonary embolism, all Grade 4.

Reversible Posterior Leukoencephalopathy Syndrome. There have been reports (<1%), some fatal, of subjects presenting with seizures and radiological evidence of reversible posterior leukoencephalopathy syndrome (RPLS). None of these subjects had a fatal outcome to the event. Patients with seizures and signs/symptoms consistent with RPLS, such as hypertension, headache, decreased alertness, altered mental functioning, and visual loss, including cortical blindness should be controlled with medical management including control of hypertension. Temporary suspension of SUTENT is recommended; following resolution, treatment may be resumed at the discretion of the treating physician.

Pancreatic and Hepatic Function. If symptoms of pancreatitis or hepatic failure are present, patients should have SUTENT discontinued. Pancreatitis was observed in 5 (1%) patients receiving SUTENT for treatment-naïve RCC compared to 1 (<1%) patient receiving IFN-α. Hepatotoxicity was observed in patients receiving SUTENT *[See Boxed Warning and Warnings and Precautions].*

Post-marketing Experience. The following adverse reactions have been identified during post-approval use of SUTENT. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and lymphatic system disorders: hemorrhage associated with thrombocytopenia*. Suspension of SUTENT is recommended; following resolution, treatment may be resumed at the discretion of the treating physician.

Gastrointestinal disorders: esophagitis.

Hepatobiliary disorders: cholecystitis, particularly acalculous cholecystitis.

Immune system disorders: hypersensitivity reactions, including angioedema.

Infections and infestations: serious infection (with or without neutropenia)*; necrotizing fasciitis, including of the perineum*. The infections most commonly observed with sunitinib treatment include respiratory, urinary tract, skin infections and sepsis/septic shock.

Musculoskeletal and connective tissue disorders: fistula formation, sometimes associated with tumor necrosis and/or regression*; myopathy and/or rhabdomyolysis with or without acute renal failure*. Patients with signs or symptoms of muscle toxicity should be managed as per standard medical practice.

Renal and urinary disorders: renal impairment and/or failure*; proteinuria; rare cases of nephrotic syndrome. Baseline urinalysis is recommended, and patients should be monitored for the development or worsening of proteinuria. The safety of continued SUTENT treatment in patients with moderate to severe proteinuria has not been systematically evaluated. Discontinue SUTENT in patients with nephrotic syndrome.

Respiratory disorders: pulmonary embolism*.

Skin and subcutaneous tissue disorders: pyoderma gangrenosum, including positive dechallenges; erythema multiforme and Stevens-Johnson syndrome.

Vascular disorders: arterial thromboembolic events*. The most frequent events included cerebrovascular accident, transient ischemic attack and cerebral infarction.

*including some fatalities

DRUG INTERACTIONS

CYP3A4 Inhibitors. Strong CYP3A4 inhibitors such as ketoconazole may **increase** sunitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme inhibition potential is recommended. Concurrent administration of SUTENT with the strong CYP3A4 inhibitor, ketoconazole, resulted in 49% and 51% increases in the combined (sunitinib + primary active metabolite) C_{max} and $AUC_{0-\infty}$ values, respectively, after a single dose of SUTENT in healthy volunteers. Co-administration of SUTENT with strong inhibitors of the CYP3A4 family (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) may increase sunitinib concentrations. Grapefruit may also increase plasma concentrations of sunitinib. A dose reduction for SUTENT should be considered when it must be co-administered with strong CYP3A4 inhibitors *[see Dosage and Administration].*

CYP3A4 Inducers. CYP3A4 inducers such as rifampin may **decrease** sunitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme induction potential is recommended. Concurrent administration of SUTENT with the strong CYP3A4 inducer, rifampin, resulted in a 23% and 46% reduction in the combined (sunitinib + primary active metabolite) C_{max} and $AUC_{0-\infty}$ values, respectively, after a single dose of SUTENT in healthy volunteers. Co-administration of SUTENT with inducers of the CYP3A4 family (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, St. John's Wort) may decrease sunitinib concentrations. St. John's Wort may decrease sunitinib plasma concentrations unpredictably. Patients receiving SUTENT should not take St. John's Wort concomitantly. A dose increase for SUTENT should be considered when it must be co-administered with CYP3A4 inducers *[see Dosage and Administration].*

In Vitro Studies of CYP Inhibition and Induction. *In vitro* studies indicated that sunitinib does not induce or inhibit major CYP enzymes. The *in vitro* studies in human liver microsomes and hepatocytes of the activity of CYP isoforms CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, and CYP4A9/11 indicated that sunitinib and its primary active metabolite are unlikely to have any clinically relevant drug-drug interactions with drugs that may be metabolized by these enzymes.

USE IN SPECIFIC POPULATIONS

Pregnancy. Pregnancy Category D *[see Warnings and Precautions].*
Sunitinib was evaluated in pregnant rats (0.3, 1.5, 3.0, 5.0 mg/kg/day) and rabbits (0.5, 1, 5, 20 mg/kg/day) for effects on the embryo. Significant increases in the incidence of embryolethality and structural abnormalities were observed in rats at the dose of 5 mg/kg/day (approximately 5.5 times the systemic exposure [combined AUC of sunitinib + primary active metabolite] in patients administered the recommended daily doses [RDD]). Significantly increased embryolethality was observed in rabbits at 5 mg/kg/day while developmental effects were observed at ≥1 mg/kg/day (approximately 0.3 times the AUC in patients administered the RDD of 50 mg/day). Developmental effects consisted of fetal skeletal malformations of the ribs and vertebrae in rats. In rabbits, cleft lip was observed at 1 mg/kg/day and cleft lip and cleft palate were observed at 5 mg/kg/day (approximately 2.7 times the AUC in patients administered the RDD). Neither fetal loss nor malformations were observed in rats dosed at ≤3 mg/kg/day (approximately 2.3 times the AUC in patients administered the RDD).

Sunitinib (0.3, 1.0, 3.0 mg/kg/day) was evaluated in a pre- and postnatal development study in pregnant rats. Maternal body weight gains were reduced during gestation and lactation at doses ≥1 mg/kg/day but no maternal reproductive toxicity was observed at doses up to 3 mg/kg/day (approximately 2.3 times the AUC in patients administered the RDD). At the high dose of 3 mg/kg/day, reduced body weights were observed at birth and persisted for offspring of both sexes during the pre-weaning period and in males during post-weaning period. No other developmental toxicity was observed at doses up to 3 mg/kg/day (approximately 2.3 times the AUC in patients administered the RDD).

Nursing Mothers. Sunitinib and its metabolites are excreted in rat milk. In lactating female rats administered 15 mg/kg, sunitinib and its metabolites were extensively excreted in milk at concentrations up to 12-fold higher than in plasma. It is not known whether this drug or its primary active metabolite are 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 SUTENT, 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 SUTENT in pediatric patients have not been established.

Physeal dysplasia was observed in cynomolgus monkeys with open growth plates treated for ≥ 3 months (3 month dosing 2, 6, 12 mg/kg/day; 8 cycles of dosing 0.3, 1.5, 6.0 mg/kg/day) with sunitinib at doses that were >0.4 times the RDD based on systemic exposure (AUC). In developing rats treated continuously for 3 months (1.5, 5.0 and 15.0 mg/kg) or 5 cycles (0.3, 1.5, and 6.0 mg/kg/day), bone abnormalities consisted of thickening of the epiphyseal cartilage of the femur and an increase of fracture of the tibia at doses ≥ 5 mg/kg (approximately 10 times the RDD based on AUC). Additionally, caries of the teeth were observed in rats at >5 mg/kg. The incidence and severity of physeal dysplasia were dose-related and were reversible upon cessation of treatment; however, findings in the teeth were not. A no effect level was not observed in monkeys treated continuously for 3 months, but was 1.5 mg/kg/day when treated intermittently for 8 cycles. In rats the no effect level in bones was ≤ 2 mg/kg/day.

Geriatric Use. Of 825 GIST and RCC patients who received SUTENT on clinical studies, 277 (34%) were 65 and over. No overall differences in safety or effectiveness were observed between younger and older patients.

Hepatic Impairment. No dose adjustment to the starting dose is required when administering SUTENT to patients with Child-Pugh Class A or B hepatic impairment. Sunitinib and its primary metabolite are primarily metabolized by the liver. Systemic exposures after a single dose of SUTENT were similar in subjects with mild or moderate (Child-Pugh Class A and B) hepatic impairment compared to subjects with normal hepatic function. SUTENT was not studied in subjects with severe (Child-Pugh Class C) hepatic impairment. Studies in cancer patients have excluded patients with ALT or AST >2.5 x ULN or, if due to liver metastases, >5.0 x ULN.

Renal Impairment. No adjustment to the starting dose is required when administering SUTENT to patients with mild, moderate, and severe renal impairment. Subsequent dose modifications should be based on safety and tolerability *[see Dose Modification].* In patients with end-stage renal disease (ESRD) on hemodialysis, no adjustment to the starting dose is required. However, compared to subjects with normal renal function, the sunitinib exposure is 47% lower in subjects with ESRD on hemodialysis. Therefore, the subsequent doses may be increased gradually up to 2 fold based on safety and tolerability.

OVERDOSAGE

Treatment of overdose with SUTENT should consist of general supportive measures. There is no specific antidote for overdosage with SUTENT. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage. Cases of accidental overdose have been reported; these cases were associated with adverse reactions consistent with the known safety profile of SUTENT, or without adverse reactions. A case of intentional overdose involving the ingestion of 1,500 mg of SUTENT in an attempted suicide was reported without adverse reaction. In non-clinical studies mortality was observed following as few as 5 daily doses of 500 mg/kg (3000 mg/m^2) in rats. At this dose, signs of toxicity included impaired muscle coordination, head shakes, hypoactivity, ocular discharge, piloerection and gastrointestinal distress. Mortality and similar signs of toxicity were observed at lower doses when administered for longer durations.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility. The carcinogenic potential of sunitinib has been evaluated in two species: rasH2 transgenic mice and Sprague-Dawley rats. There were similar positive findings in both species. In rasH2 transgenic mice gastroduodenal carcinomas and/or gastric mucosal hyperplasia, as well as an increased incidence of background hemangiosarcomas were observed at doses of ≥25 mg/kg/day following daily dose administration of sunitinib in studies of 1- or 6-months duration. No proliferative changes were observed in rasH2 transgenic mice at 8 mg/kg/day. Similarly, in a 2-year rat carcinogenicity study, administration of sunitinib in 28-day cycles followed by 7-day dose-free periods resulted in findings of duodenal carcinoma at doses as low as 1 mg/kg/day (approximately 0.9 times the AUC in patients given the RDD of 50 mg/day). At the high dose of 3 mg/kg/day (approximately 7.8 times the AUC in patients at the RDD of 50 mg/day) the incidence of duodenal tumors was increased and was accompanied by findings of gastric mucous cell hyperplasia and by an increased incidence of pheochromocytoma and hyperplasia of the adrenal medulla. Sunitinib did not cause genetic damage when tested in *in vitro* assays (bacterial mutation [AMES Assay], human lymphocyte chromosome aberration) and an *in vivo* rat bone marrow micronucleus test.

Effects on the female reproductive system were identified in a 3-month repeat dose monkey study (2, 6, 12 mg/kg/day), where ovarian changes (decreased follicular development) were noted at 12 mg/kg/day (≥ 5.1 times the AUC in patients administered the RDD), while uterine changes (endometrial atrophy) were noted at ≥2 mg/kg/day (≥ 0.4 times the AUC in patients administered the RDD). With the addition of vaginal atrophy, the uterine and ovarian effects were reproduced at 6 mg/kg/day in the 9-month monkey study (0.3, 1.5 and 6 mg/kg/day administered daily for 28 days followed by a 14 day respite; the 6 mg/kg dose produced a mean AUC that was ≥ 0.8 times the AUC in patients administered the RDD). A no effect level was not identified in the 3 month study; 1.5 mg/kg/day represents a no effect level in monkeys administered sunitinib for 9 months.

Although fertility was not affected in rats, SUTENT may impair fertility in humans. In female rats, no fertility effects were observed at doses of ≤5.0 mg/kg/day [(0.5, 1.5, 5.0 mg/kg/day) administered for 21 days up to gestational day 7; the 5.0 mg/kg dose produced an AUC that was ≥ 5 times the AUC in patients administered the RDD], however significant embryolethality was observed at the 5.0 mg/kg dose. No reproductive effects were observed in male rats dosed (1, 3 or 10 mg/kg/day) for 58 days prior to mating with untreated females. Fertility, copulation, conception indices, and sperm evaluation (morphology, concentration, and motility) were unaffected by sunitinib at doses ≤10 mg/kg/day (the 10 mg/kg/day dose produced a mean AUC that was ≥ 25.8 times the AUC in patients administered the RDD).

PATIENT COUNSELING INFORMATION

Gastrointestinal Disorders. Gastrointestinal disorders such as diarrhea, nausea, stomatitis, dyspepsia, and vomiting were the most commonly reported gastrointestinal events occurring inpatients who received SUTENT. Supportive care for gastrointestinal adverse events requiring treatment may include anti-emetic or anti-diarrheal medication.

Skin Effects. Skin discoloration possibly due to the drug color (yellow) occurred in approximately one third of patients. Patients should be advised that depigmentation of the hair or skin may occur during treatment with SUTENT. Other possible dermatologic effects may include dryness, thickness or cracking of skin, blister or rash on the palms of the hands and soles of the feet. Severe dermatologic toxicities including Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis have been reported. Patients should be advised to immediately inform their healthcare provider if severe dermatologic reactions occur.

Other Common Events. Other commonly reported adverse events included fatigue, high blood pressure, bleeding, swelling, mouth pain/irritation and taste disturbance.

Osteonecrosis of the Jaw. Prior to treatment with SUTENT, a dental examination and appropriate preventive dentistry should be considered. In patients being treated with SUTENT, who have previously received or are receiving bisphosphonates, invasive dental procedures should be avoided, if possible.

Hypoglycemia. Patients should be advised of the signs, symptoms, and risks associated with hypoglycemia that may occur during treatment with SUTENT. Hypoglycemia may be more severe in patients with diabetes taking antidiabetic medications. Severe hypoglycemia including loss of consciousness or requiring hospitalization has been reported. Patients should be advised to immediately inform their healthcare provider if severe signs or symptoms of hypoglycemia occur.

Thrombotic Microangiopathy. Thrombotic microangiopathy leading to renal insufficiency and neurologic abnormalities was observed in patients who received SUTENT as monotherapy or in combination with bevacizumab. Patients should be advised that signs and symptoms of thrombotic microangiopathy may occur during treatment with SUTENT. Patients should be advised to immediately inform their healthcare provider if signs and symptoms of thrombotic microangiopathy occur.

Proteinuria. Proteinuria and nephrotic syndrome has been reported. Patients should be advised that urinalysis will be performed prior to starting as well as during treatment with SUTENT. In cases with impact to renal function, treatment with SUTENT may be interrupted or discontinued.

Concomitant Medications. Patients should be advised to inform their health care providers of all concomitant medications, including over-the-counter medications and dietary supplements *[see Drug Interactions]*.

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ASCO GU Provides Insightful, Provocative Updates on Broad Spectrum of RCC

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This is a time capsule from the Genitourinary Cancers Symposium held in San Francisco, January 7-9, 2016. Selected abstracts from the sessions offer an intriguing snapshot and a multi-faceted view of current directions in diagnosis and therapy. The content of each abstract is briefly summarized and the possible implication provided to facilitate your review. All of the abstracts in renal cell carcinoma from the scientific sessions may be viewed at this ASCO website: http://meetinglibrary.asco.org/abstractbysubcategory/2016%20Genitourinary%20Cancers%20Symposium/40

When a scientific meeting generates 19 presentations and 129 posters focused on kidney cancer, the challenge of highlighting the key findings is formidable indeed. How does one select from such an abundance of high-quality data, regardless of the topic? The 2016 ASCO GU meeting presented such a challenge with investigators covering virtually every topic relevant to renal cell carcinoma (RCC), from combinations of treatments to new considerations in surgery, from advances in genomic studies to new insights on the use checkpoint inhibitors, and much more.

Although no new phase III clinical trial data were presented at this year's Symposium, longer-term follow-up and subgroup analyses of recently published trials, as well as new genomic and translational studies were presented. *(Editor's note: The full abstracts to all RCC presentations at ASCO GU are available online at the link mentioned above.)* Updating and elucidating many trends already apparent from last year's general ASCO and ESMO meetings, the GU sessions covered a broad spectrum of topics in sessions that were heavily attended.

The following highlights touch upon a dynamic and diverse group of presentations likely to reflect trends at future meetings:

Role of cytoreductive nephrectomy in renal cell cancer (RCC) with venous tumor thrombus. [Abstract 496

Abel EJ et al addressed the issue of RCC with tumor thrombus, particularly in the setting of distant metastatic disease; RCC with tumor thrombus may require complex surgery to remove the primary tumor and associated thrombus, and this study evaluated the role of such an extensive surgery in these patients with potentially poor prognosis, as it is unclear what patients could benefit from surgical intervention. The study collected data on 293 patients treated surgically from 2000-2014 in 4 academic medical centers. The authors noted that median overall survival (IQR) was worse for patients with IVC thrombus above the diaphragm 6.8 (2.2-19.1) months compared to renal vein only thrombus 18.8 (8.1-37.8) months, or IVC thrombus below the diaphragm 18.9 (6.7-44.5) months. Using MDACC criteria (Culp et al. Cancer 2010), patients were categorized into either favorable risk (258) or unfavorable risk (35) groups. Median OS was higher (P = 0.008) in favorable risk patients, 18.8 (7.2-43.7) vs. 8.2 (2.3-28.2) months. On multivariable analysis, preoperative variables that were predictors of OS included IVC thrombus above diaphragm, lactate dehydrogenase > upper limit of normal, and retroperitoneal lymphadenopathy.

Take-home: Patients with metastatic RCC and tumor thrombus might not benefit from surgery if the IVC thrombus is above the diaphragm (level IV) or if they have unfavorable risk based on MDACC criteria.

CheckMate 025 phase III trial: Outcomes by key baseline factors and prior therapy for nivolumab (NIVO) versus everolimus (EVE) in advanced renal cell carcinoma (RCC). [Abstract 498]

Results from this pivotal trial (that was stopped early as it

had met its primary endpoint of overall survival) were reviewed by Motzer et al, once again confirming the benefits of nivolumab when key baseline factors and prior therapy are considered as variables and endpoints for nivolumab are compared with everolimus. In patients who had prior sunitinib, median overall survival was 23.6 months for nivolumab vs 19.8 months for everolimus; in those who had prior pazopanib, median OS was not estimable for nivolumab vs 17.6 months for everolimus. For those who had prior IL-2 (10%), median OS was not estimable for nivolumab vs 17.2 months for everolimus.

Take-home: In addition to the previously demonstrated superiority of nivolumab over everlimus in the second-line setting (CheckMate 025), the current study confirmed the superiority of nivolumab (both for overall survival and overall response rate) independent of baseline factors such as Karnofsky performance status, IMDC risk group, and number of prior therapies. In addition, this superiority was maintained irrespective of prior therapies such as sunitinib, pazopanib, and Interleukin-2.

Subgroup analyses of METEOR, a randomized phase 3 trial of cabozantinib versus everolimus in patients (pts) with advanced renal cell carcinoma (RCC). [Abstract 499]

In a review of their findings, Escudier et al reaffirmed the efficacy of cabozantinib versus everolimus in the published clinical trial (PFS determined by independent review of all 658 enrolled patients was 7.4 months for cabozantinib versus 3.9 months for everolimus, HR=0.52, $P<0.001$). In addition, they studied the differences in endpoints among patient subgroups, and noted that the benefit of cabozantinib was present irrespective of ECOG PS (trial only included PS 0 and 1), sum of target lesion size, presence of lung or liver or bone metastasis, number of prior VEGFR TKIs received, type of VEGFR TKI received, and whether patients received PD-1/PD-L1 therapy or not. The benefit however was noted mainly in MSKCC favorable and intermediate risk groups (not statistically different in poor risk group).

Take-home: The METEOR phase 3 trial has met its primary endpoint of significant improvement in PFS with cabozantinib vs everolimus in the full study cohort, with a trend in improvement in overall survival, although longer follow-up is still needed for this secondary endpoint. The improvement in PFS was noted independent of ECOG PS, site of metastatic disease, tumor burden, type of prior therapy, and mostly noted in MSKCC good and intermediate risk groups.

Immunomodulation by HDAC inhibition: Results from a phase II study with entinostat and high-dose Interleukin 2 in renal cell carcinoma patients. [Abstract 500]

Pili et al reported on an ongoing single arm phase I/II trial using the combination of ertinostat (a class I HDAC inhibitor) with high-dose Interleukin-2. The study primary objectives were to evaluate the safety, tolerability and efficacy of the combination, in patients with clear cell RCC who are fit enough to receive IL-2 therapy. The hypothesis behind the study is that IL-2 efficacy could be limited by immunosuppressive factors such as Tregs or MDSCs, and that ertinostat can modulate these factors, as shown in preclinical studies. The reported study included 39 enrolled patients, with 35 patients having completed one cycle of combined therapy. No severe adverse events were seen in the first 6 weeks of therapy. Twelve patients achieved an objective response (39%; 9 partial responses, 3 complete responses) with a median time to response of 81 days (55-96). The median PFS has not been reached yet (median follow-up = 437 days). Preliminary translational studies show decreased Tregs and MDSCs after combined treatment.

Take-home: Ertinostat and IL-2 combination appears to be safe and tolerated, with signs of efficacy (39% response rate) in this phase II clinical trial.

Phase II study of axitinib for downstaging cT2a to cT1 renal tumors for allowing partial nephrectomy (AXIPAN). [Abstract 575]

Patard et al performed a prospective phase II study to investigate whether axitinib can downsize large tumors and allow for partial nephrectomy instead of a radical nephrectomy. The study enrolled 18 patients with biopsy-proven clear cell RCC, clinical stage T2a. Patients were treated with axitinib for 2-6 months (12 patients were treated for 2 months, 3 for 4 months, and 3 for 6 months). Median tumor size at baseline was 7.5cm and RENAL score was 11. After neoadjuvant axitinib, median tumor size and RENAL score decreased to 6.2 cm and 10, respectively. 88.9 % of patients had a decrease in maximum tumor diameter, with median maximum tu-mor size reduction of 1.45cm. Sixteen of the 17 patients who had surgery underwent a partial nephrectomy. 7 patients (41.2%) had pathologic T3a disease, and 2 patients (11.8%) had positive surgical margins. Medical and surgical complications rate was 11% including 1 embolization for severe bleeding and 1 death at 1 month after surgery due to myocardial infarction.

Take-home: Neoadjuvant axitinib in cT2a clear cell RCC results in downsizing of tumors. Nephron sparing surgery was possible in the majority of patients, although it remained technically complex, requiring extensive surgical expertise. It is unclear from this study, however, how many patients could have undergone partial nephrectomy without axitinib treatment.

Pazopanib for treatment of metastatic renal cell carcinoma with non-clear cell histology: Single-arm, open label, multicenter, phase II study. [Abstract 577]

Sun Jung et al conducted a single-arm, phase 2 study that

enrolled 29 patients with metastatic non-clear cell RCC (sarcomatoid features or collecting duct carcinoma were excluded). Patients received pazopanib daily until progression of disease or intolerable toxicity was observed. The primary objectives were progression free survival with secondary objectives of overall survival, treatment response and safety profiles. The median PFS was 8.3 months (95% CI, 4.0-12.6 months) and median OS was not reached (range, 1.5-34.7 months). Five patients (17.2%) were still receiving treatment without disease progression. Sixteen patients (55.2%) experienced disease progression and 8 patients (27%) died during the study. There were no treatment-related deaths.

Take-home: Pazopanib shows promising activity (PFS 8.3 months) with tolerable adverse events in patients with non-clear cell RCC, a group that includes patients with papillary and chromophobe RCC, for whom no standard therapy exists yet.

Genomic characterization of sarcomatoid transformation in clear cell renal cell carcinoma. [Abstract 509]

Renal cell carcinoma with sarcomatoid dedifferentiation is a very aggressive tumor, with poor prognosis, yet genomic studies on this tumor have been limited. Bi et al performed exome sequencing on paired epithelial/sarcomatoid/normal areas in 21 patients with clear cell RCC. Sarcomatoid regions appeared to have a greater mutation burden ($P = 4.0x10^{-4}$). Two tumors showed evidence of hypermutation. A low percentage (57.9%) of tumors had mutations in *VHL*. Mutations in *PBRM1, PTEN, SETD2, ARID1A,* and *BAP1* were common. Interestingly, all mutations in *ARID1A* and *BAP1* were specific to sarcomatoid areas. *TP53* mutations were observed in 31.5% of patients, specifically in the sarcomatoid areas, concurrent with loss of heterozygosity.

Take-home: Tumors from patients with clear cell RCC with sarcomatoid dedifferentiation show evidence of hypermutation. In addition, the sarcomatoid component exhibits a higher mutational burden of cancer driver genes. Finally, *TP53* mutation was frequent and appeared to be limited to the sarcomatoid component.

Comprehensive genomic profiling of renal cell carcinoma with sarcomatoid dedifferentiation to pinpoint recurrent genomic alterations. [Abstract 537]

Another study offered further insights on genomic alterations in patients with renal cell carcinoma with sarcomatoid dedifferentiation (sRCC). Genomic profiling was performed initially on paired samples (sarcomatoid/epithelioid) from 3 patients with clear cell RCC with sarcomatoid dedifferentiation, and then on another 23 sRCC harboring diverse epithelioid components. Genomic profiling was conducted using a next generation DNA sequencing assay of 236 cancer-related genes and 19 genes frequently rearranged in cancer. Results were compared with 56 similarly sequenced cases of clear cell RCC without any sarcomatoid component, and with clear cell, chromophobe, and papillary TCGA. Two of three sRCC cases that underwent CGP of both their epithelial and the sarcomatoid components demonstrated identical mutational profiles, and a third case demonstrated commonly disrupted genes. The most frequent altered genes in the other 23 patients were *TP53*(43%), *CDKN2A*(30%), *VHL*(26%) and *NF2*(22%). *NF2* mutations were mutually exclusive with *TP53* but not with *VHL* mutations.

Take-home: sRCC contains different driver mutations than non-sarcomatoid RCC. The level of *TP53* and *NF2* mutation is impressive and can be harnessed for potential therapeutic interventions, although further larger studies are needed to determinethe implications of these findings. Targeting the Hippo pathway should be evaluated in patients with *NF2* mutations.

Understanding the genomic underpinnings of metastatic chromophobe renal cell carcinoma. [Abstract 513]

Casuscelli et al used a cohort of 40 patients with metastatic chromophobe RCC from 3 academic institutions and performed whole genome sequencing in 6 patients, and targeted next generation sequencing in 33 patients (42 samples). Matched primary and metastatic tumors from 7 patients were analysed. 27 non-metastatic chromophobe RCC tumors were used as control and underwent targeted sequencing. The most commonly mutated genes in the aggressive chRCC tumors were *TP53* and *PTEN* (*TP53* 61%, *PTEN* 27%, using targeted sequencing). Primary tumor samples showed the typical pattern of chromosomal losses in 1, 2, 6, 10, 13 and 17, confirming chromophobe TCGA findings. Surprisingly, these chromosomal losses were not detected in the meta-static sites.

Take-home: *TP53* and *PTEN* mutations are highly prevalent in patients with chromophobe RCC, including those with metastatic disease. The finding of differences in chromosomal loss pattern between primary tumors and metastatic sites is novel and is being further investigated by the authors using different analytical platforms.

Mutation burden and tumor neoantigens in RCC patients (pts) treated with nivolumab. [Abstract 514]

Voss et al performed whole exome sequencing and RNAseq on RCC samples (frozen pre-treatment tumor/normal tissue) from 8 patients treated with nivolumab (7 nivolumab only, 1 ipilimumab/nivolumab followed by nivolumab). Two of 7 Nivo-monotherapy patients achieved durable clinical benefit (DCB, defined as partial response > 12 months); 1 had a non-durable partial response (5 months). For 2 nivolumab /DCB pts, the burden of non-synonymous somatic mutations was higher compared to those with no DCB. The ratio of predicted neoantigens/total mutations was higher for patients with

DCB/Objective response compared to those with progressive disease. RNASeq results were different for DCB vs. non-DCB pts in several genes, including mediators of antigen presentation to T-cells (HLA-A, -B, -C; B2M) and composition of other immune regulators (CSF1R, LGALS1), but interestingly, not for PDL1.

Take-home: Somatic mutations, especially those that result in tumor neoantigens, may be predictive of response to nivolumab, and should be studied in larger cohorts.

Integrated genomic correlates of response to PD-1 inhibitor nivolumab in metastatic renal cell carcinoma (mRCC). [Abstract 545]

Similarly, de Velasco et al performed whole exome sequencing in 9 patients treated with nivolumab for metastatic clear cell RCC (using pre-treatment frozen tissue from metastatic sites), and RNAseq in 6 of these patients. Per RECIST, 3 were responders and 6 were not. The authors found that neoantigen load was significantly higher in non-responders compared to responders, however, the non-synonymous mutation load was not different. An exceptional responder (complete responder for over 30 months) had outlying higher expression of selected immune-related genes compared to the 8 other patients.

Take-home: This study found that responders and non-responders differed in neoantigen load, but not in non-synonymous mutation load, in contradistinction to the above study.

Clinical, pathologic, and genomic profiles of exceptional responders to anti–PD1 therapy in renal cell carcinoma. [Abstract 625]

In a similar theme, Ball et al studied 7 patients treated with anti-PD-1 therapy, using tumor expression of PD-L1, infiltrating CD8+ lymphocytes, whole exome sequencing, and Nanostring. They compared 4 exceptional responders (complete response or almost-complete response at 24 months after therapy) with 3 primary refractory patients. They noted that exceptional responders had trends toward higher CD8+ lymphocyte infiltration, higher number of somatic mutations, and higher number of predicted mutation associated neoantigens as compared with primary refractory patients. In addition, RNA expression analysis revealed a higher expression of T cell and innate immune signatures, whereas primary refractory patients had more of an acute phase and immune tolerance signature.

Take-home: Exceptional responders to anti-PD-1 therapy demonstrate a higher number of CD8+ lymphocyte infiltration, neoantigens, and somatic mutations, compared to refractory patients. It is important to keep in mind that some of the differences in the 3 studies above could be related to the small sample size, heterogeneity of the cohorts, and the different definitions for the primary endpoint used in the analyses.

Clear cell renal cell carcinoma (ccRCC) is among the most highly infiltrated tumors despite a relatively low mutation burden. [Abstract 605]

Winer et al utilized an RNAseq-based aggregate immune score to compare immune infiltration levels across 20 tumor types studied in The Cancer Genome Atlas (TCGA) and then validated results with an independent cohort of 101 patients with clear cell RCC. The authors identified clear cell RCC as an outlier from an immune standpoint, that differs from other highly infiltrated tumors in its overexpression of antigen presentation machinery. Three unique clusters of tumors emerged in the 415 patients with clear cell RCC in TCGA cohort, primarily separated by varying degrees of T cell infiltration; coined (1) T-cell-enriched, (2) heterogeneous, and (3) non-infiltrated groups, and these clusters were validated in the independent cohort. A comparison of the degree of clonality with immune infiltration levels revealed that tumors with less intratumoral heterogeneity had higher immune infiltration in both cohorts.

Take-home: The study suggests a novel insight into the immune landscape of ccRCC tumors and divides patients with clear cell RCC into different groups, based on the degree of T cell infiltration.

Comparing surgical tissue versus biopsy tissue in the development of a clear cell renal cell carcinoma xenograft model. [Abstract 519]

Dong et al explored the potential of a personalized xenograft model using pretreatment tissue for patients with advanced kidney cancer. The study included 56 specimens from 48 patients with clear cell RCC. Tissue was obtained either during surgery (35 patients) or from biopsies (21 patients). Tissues were implanted subcutaneously in immunodeficient mice and followed for up to 4 months. Quality assurance was performed to document tumor histology; 25 of the 56 tumor specimens were able to grow in immunodeficient mice. Interestingly, biopsy tissue was more successful compared to surgical tissue, 61.9% versus 34.2%.

Take-home: Xenograft models can be successfully achieved in a number of patients with clear cell RCC, using either surgical specimens, or more interestingly, biopsy specimens. This could be helpful for patient selection for specific therapies, and for monitoring of genomic changes during treatment to find correlates of response and resistance to therapy. KCJ

EDITOR'S MEMO

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on intriguing results.

And what about chemotherapy? Its track record in RCC is largely disappointing. But that was before nanoparticle technology became more of a gleam in a researcher's eye. Nanoparticle technology could potentially be used to deliver a payload of chemotherapy and a TKI to the tumor cell, bypassing normal cells. It is not a vision but a premise being investigated in a Phase 2 trial now fully accrued to study the effects of nanoparticle technology on tumor cell permeability.

Expectations surrounding this trial are high in view of positive data gained in a Phase 1b/2 study in which the nanoparticle conjugate developed by Cerulean was also evaluated and showed promise for extending progression-free survival. The Phase 2 trial compares CRLX101 in combination with bevacizumab to investigator's choice of standard of care (SOC) in patients with RCC who have received two or three prior lines of therapy. Results may not be available until 2017, but if the favorable results seen in preliminary investigations can be validated there could be one more option to improve the therapeutic ratio in RCC.

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(HR) of 0.97, while an unadjusted analysis resulted in an OS HR of 1.96. The head-to-head trial reported a final OS HR of 0.92 for pazopanib versus sunitinib.
Conclusion: This case study supports the need to adjust for confounded OS due to crossover, which enables trials to meet ethical standards and provides decision makers with a more accurate estimate of treatment benefit.

Genomic characterization of sarcomatoid transformation in clear cell renal cell carcinoma. Bi M, Zhao S, Said JW, et al. *Proc Natl Acad Sci USA*. 2016 Feb 23; 113(8):2170-5. doi: 10.1073/pnas.1525735113.
Summary: The presence of sarcomatoid features in clear cell renal cell carcinoma (ccRCC) confers a poor prognosis and is of unknown pathogenesis. This study performed exome sequencing of matched normal-carcinomatous-sarcomatoid specimens from 21 subjects. Two tumors had hypermutation consistent with mismatch repair deficiency. In the remainder, sarcomatoid and carcinomatous elements shared 42% of somatic single-nucleotide variants (SSNVs). Sarcomatoid elements had a higher overall SSNV burden (mean 90 vs. 63 SSNVs, $P = 4.0 \times 10(-4)$), increased frequency of nonsynonymous SSNVs in Pan-Cancer genes (mean 1.4 vs. 0.26, $P = 0.002$), and increased frequency of loss of heterozygosity (LOH) across thegenome (median 913 vs. 460 Mb in LOH, $P < 0.05$), with significant recurrent LOH on chromosomes 1p, 9, 10, 14, 17p, 18, and 22. The most frequent SSNVs shared by carcinomatous and sarcomatoid elements were in known ccRCC genes including von Hippel-Lindau tumor suppressor (VHL), polybromo 1 (PBRM1), SET domain containing 2 (SETD2), phosphatase and tensin homolog (PTEN). Most interestingly, sarcomatoid elements acquired biallelic tumor protein p53 (TP53) mutations in 32% of tumors ($P = 5.47 \times 10(-17)$); TP53 mutations were absent in carcinomatous elements in nonhypermutated tumors and rare in previously studied ccRCCs. Mutations in known cancer drivers AT-rich interaction domain 1A (ARID1A) and BRCA1 associated protein 1 (BAP1) were significantly mutated in sarcomatoid elements and were mutually exclusive with TP53 and each other.
Conclusion: These findings provide evidence that sarcomatoid elements arise from dedifferentiation of carcinomatous ccRCCs and implicate specific genes in this process. These findings have implications for the treatment of patients with these poor-prognosis cancers.

Mutations in TSC1, TSC2, and MTOR are associated with response to rapalogs in patients with metastatic Renal Cell Carcinoma. Kwiatkowski DJ, Choueiri TK, Fay AP, et al. *Clin Cancer Res*. 2016 Feb 1. clincanres.2631.2015
Summary: The hypothesis was that mutations in mTOR pathway genes are associated with response to rapalogs in metastatic renal cell carcinoma (mRCC). The study cohort consisted of mRCC patients who were treated with mTOR inhibitors with distinct clinical outcomes. Tumor DNA from 79 subjects was successfully analyzed for mutations using targeted next generation sequencing of 560 cancer genes. Responders were defined as those with partial response (PR) by RECIST v1.0 or stable disease with any tumor shrinkage for six months or longer. Non-responders were defined as those with disease progression during the first three months of therapy. Fisher's exact test assessed the association between mutation status in mTOR pathway genes and treatment response. Mutations in MTOR, TSC1 or TSC2 were more common in responders, 12 (28%) of 43, than non-responders, 4 (11%) of 36 (P=0.06). Mutations in TSC1 or TSC2 alone were also more common in responders, 9 (21%), than non-responders, 2(6%), (P=0.05). Furthermore, 5 (42%) of 12 subjects with PR had mutations in MTOR, TSC1 or TSC2 compared to 4 (11%) of 36 non-responders (P=0.03). Eight additional genes were found to be mutated in at least 4 of 79 tumors (5%); none were associated positively with response.
Conclusion: In this cohort of mRCC patients, mutations in MTOR, TSC1 or TSC2 were more common in patients who experienced clinical benefit from rapalogs than in those who progressed. However, a substantial fraction of responders (31 of 43, 72%) had no mTOR pathway mutation identified. KCJ

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study presented at the annual meeting of the Society of Abdominal Radiology, held in March in Waikoloa, Hawaii. Rosaleen Parsons, MD, of the Fox Chase Cancer Center in Philadelphia, and colleagues tracked outcomes for patients who collectively underwent 374 renal mass biopsies between 1999 and 2015. Core-needle biopsy was performed in 65% of patient biopsies, and 41% of those patients also had surgical resection.

According to the researchers, core-needle biopsy led to accurate diagnosis of RCC in 94% of patients who had surgery. These biopsies also identified benign tumors in 11% of patients who could then receive ongoing monitoring — instead of unnecessary surgery. However, researchers did find that renal mass biopsy led to inaccurate classification of tumor stage in 37% of patients who had surgery, putting them at risk for under-treatment. Also, 30% of patients who had biopsies and then surgery potentially had low-risk tumors.

"Combining renal mass biopsy with additional clinical pathways for the management of renal masses may help minimize over- and under-treatment risks," Parsons said. "Balancing competing risks is important and should ultimately guide individualized patient care."

Phase 2 study enrolls patients for checkpoint inhibitor trial

NEW BRUNSWICK, NJ –The Rutgers Cancer Institute of New Jersey has opened a clinical trial for patients with metastatic RCC. The study is in collaboration with the Big Ten Cancer Research Consortium. Known as BTCRC-GU14-003, the trial is examining a combination of pembrolizumab, a PD-1 or "checkpoint" inhibitor, with bevacizumab.

Pembrolizumab targets a receptor on the surface of T cells called PD-1. This receptor turns off T cells and prevents them from killing cancer cells. Pembrolizumab blocks that action, allowing T cells to remain active with an immune response against cancer. Eric A. Singer, MD, MA, FACS, urologic oncologist at Rutgers Cancer Institute and assistant professor of surgery at Rutgers Robert Wood Johnson Medical School, is the lead researcher on the study

The Phase 2 trial will determine what effects pembrolizumab in combination with bevacizumab has on patients who have not received prior therapy for metastatic RCC. For more information individuals can call the Cancer Institute's Office of Human Research Services at (732) 235-8675 or email cinjclinicaltrials@cinj.rutgers.edu. Additional information, including full eligibility criteria, is available at www.clinicaltrials.gov (clinical trial # 02348008). KCJ

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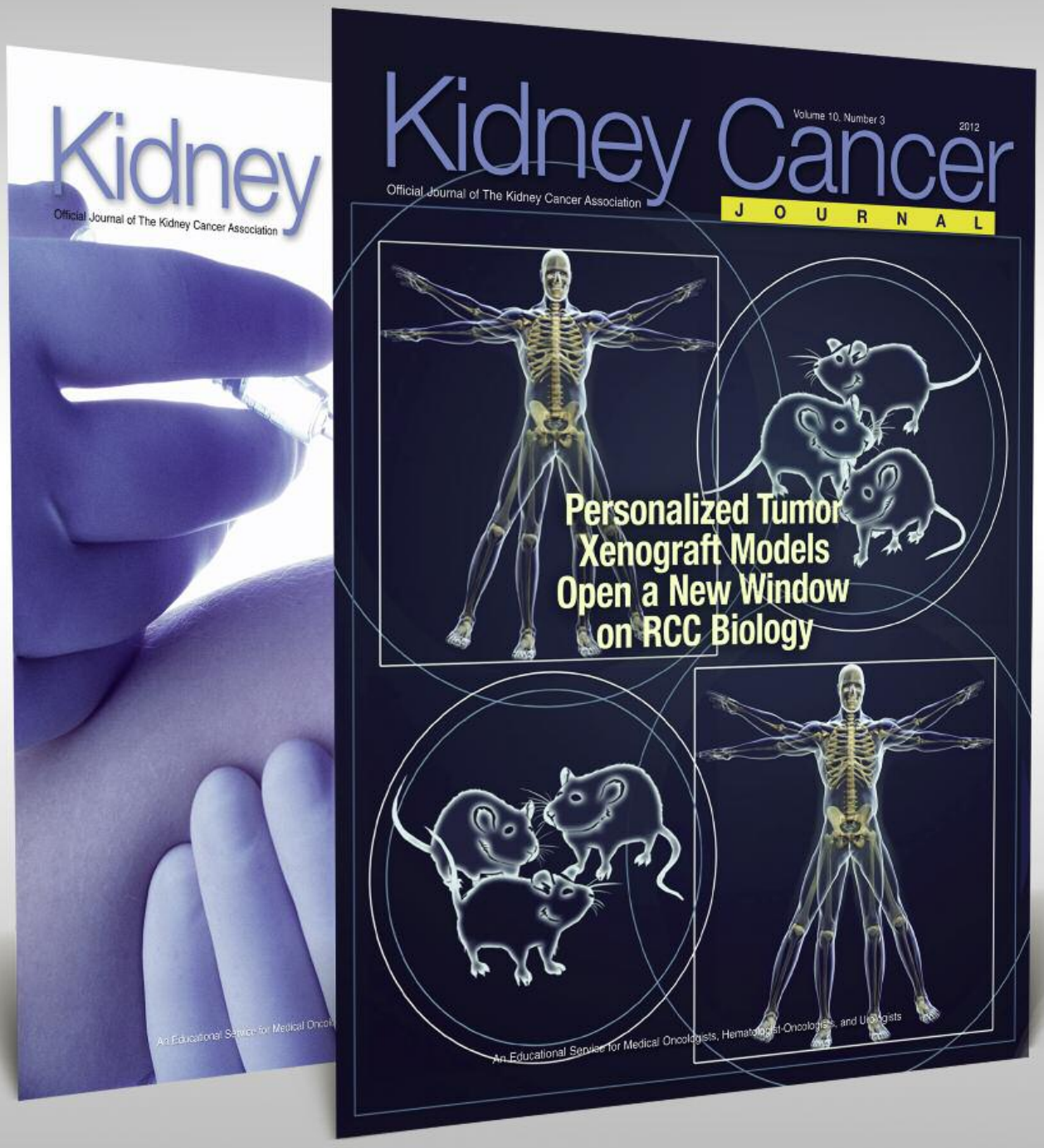

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