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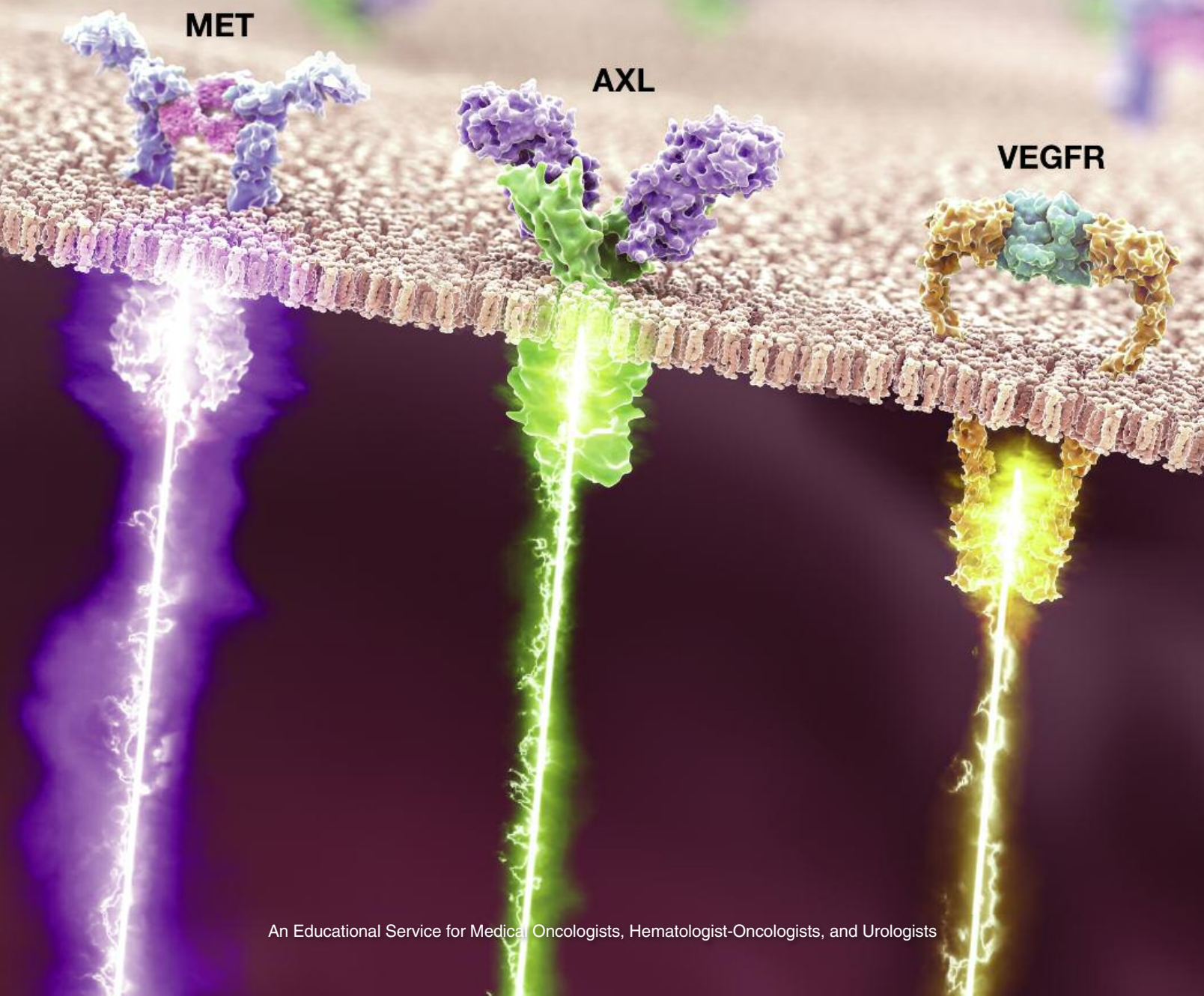
KCJ: Now in 15th Year of Publication

Milestones and Turning Points in Therapy: From the CABOSUN Trial to S-TRAC



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

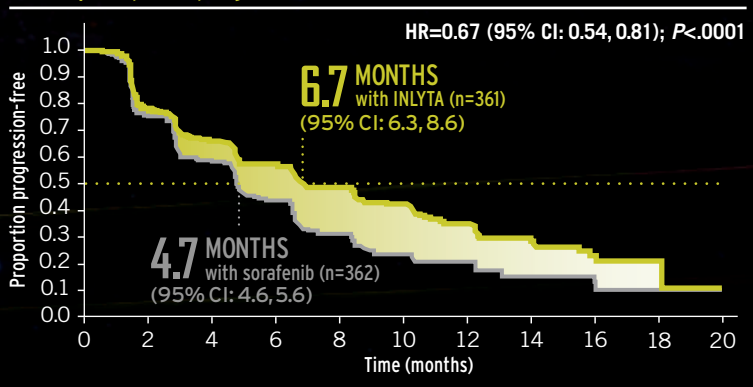
GIVE THEM A FIGHTING SECOND CHANCE

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

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

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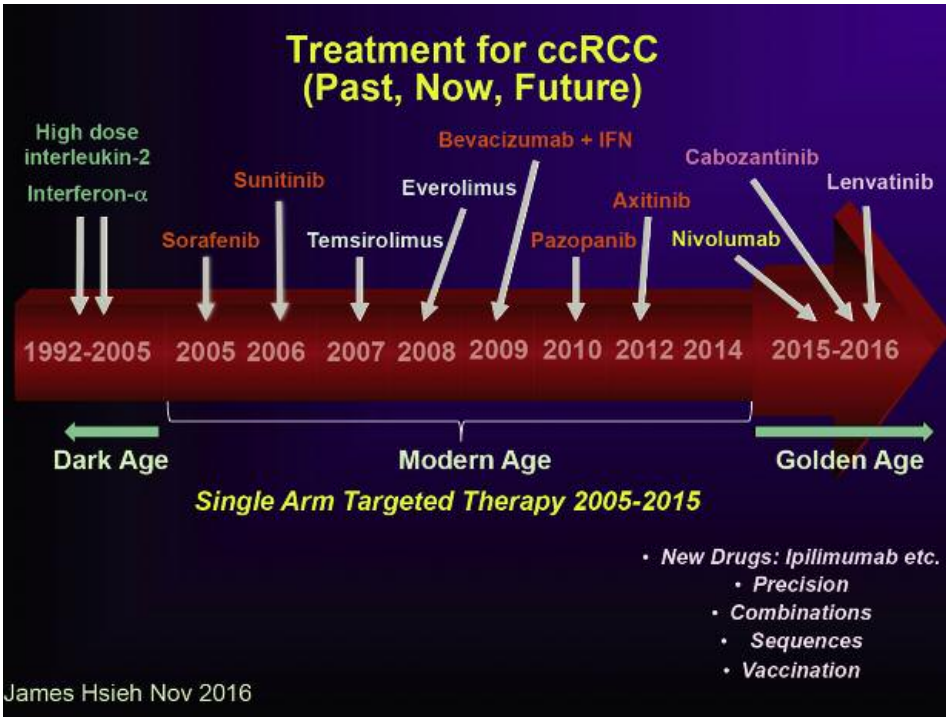
About the Cover
Dysregulation of the von Hippel-Lindau protein in RCC leads to activation of three key signaling pathways (MET, AXL, and VEGFR) targeted by cabozantinib, which was recently approved for the treatment of patients with advanced RCC who have received prior anti-angiogenic therapy.

KCJ TABLE OF CONTENTS

KCJ EDITOR'S MEMO

Advances in Treatment of RCC: Chronicling 25 Years of Progress



The timeline featured above encapsulates the progress made in the treatment of renal cell carcinoma (RCC) since 1992 when options for therapy were not only limited but associated with toxicity that deterred many patients from accepting available regimens, including interleukin-2 (IL-2) and interferon. The slide developed by James Hsieh, MD, who directs the Memorial Sloan Kettering's Translational Kidney Cancer Research Program, dramatically illustrates how far and where new directions in therapy have gone. We have seen at various points in the timeline how management strategies have ushered in what might be called "new eras" in treatment.

And, yet, as good as this timeline is in chronicling the advances made in the treatment of the disease, it is important to consider the twists and turns within these 25 years, the expectations raised by innovative approaches to the disease and yes, the setbacks and disappointments after the life cycle of various drugs revealed how challenging RCC remains and

(continued on page 139)

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.

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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.

Chromosome instability drives phenotypic switching to metastasis. Gao C, Su Y, Koeman J, et al. Proc *Natl Acad Sci USA*. 2016 Dec 5; pii:201618215

Summary: Chromosome instability (CIN) is the most striking feature of human cancers. However, how CIN drives tumor progression to metastasis remains elusive. Here we studied the role of chromosome content changes in generating the phenotypic dynamics that are required for metastasis. We isolated epithelial and mesenchymal clones from human carcinoma cell lines and showed that the epithelial clones were able to generate mesenchymal variants, which had the potential to further produce epithelial revertants autonomously. The successive acquisition of invasive mesenchymal and then epithelial phenotypes recapitulated the steps in tumor progression to metastasis. Importantly, the generation of mesenchymal variants from clonal epithelial populations was associated with subtle changes in chromosome content, which altered the chromosome transcriptome and influenced the expression of genes encoding intercellular junction (IJ) proteins, whereas the loss of chromosome 10p, which harbors the ZEB1 gene, was frequently detected in epithelial variants generated from mesenchymal clones. Knocking down these IJ genes in epithelial cells induced a mesenchymal phenotype, whereas knocking down the ZEB1 gene in mesenchymal cells induced an epithelial phenotype, demonstrating a causal role of chromosome content changes in phenotypic determination.
Conclusion: This analysis suggests a paradigm of tumor metastasis: primary epithelial carcinoma cells that lose chromosomes harboring IJ genes acquire an invasive mesenchymal phenotype, and subsequent chromosome content changes such as loss of 10p in disseminated mesenchymal cells generate epithelial variants, which can be selected for to generate epithelial tumors during metastatic colonization.

Alternating Treatment with Pazopanib and Everolimus vs Continuous Pazopanib to Delay Disease Progression in Patients with Metastatic Clear Cell Renal Cell Cancer: The ROPETAR Randomized Clinical Trial. Cirkel GA, Hamberg P, Sleijfer S, et al. *JAMA Oncol*. 2016 Dec 1. doi:10.1001/jamaoncol.2016.5202.

Summary: A total of 52 patients were randomized to the rotating arm (median [range] age, 65 [44-87] years) and 49 patients to the control arm (median [range] age, 67 [38-82] years). Memorial Sloan Kettering Cancer Center risk category was favorable in 26% of patients, intermediate in 58%, and poor in 15%. Baseline characteristics and risk categories were well balanced between arms. One-year PFS1 for rotating treatment was 45% (95% CI, 33-60) and 32% (95% CI, 21-49) for pazopanib (control). Median time until first progression or death for rotating treatment was 7.4 months (95% CI, 5.6-18.4) and 9.4 months (95% CI, 6.6-11.9) for pazopanib (control) (P=.37). Mucositis, anorexia, and dizziness were more prevalent in the rotating arm during first-line treatment. No difference in quality of life was observed.
Conclusion: Rotating treatment did not result in prolonged progression-free-survival, fewer toxic effects, or improved quality of life. First-line treatment with a vascular endothelial growth factor inhibitor remains the optimal approach in metastatic clear cell renal cell carcinoma.

Renal Cell Carcinoma Associated with Xp11.2 Translocation/TFE3 Gene Fusions: Clinical Features, Treatments and Prognosis. Liu N, Wang Z, Gan W, et al. *PLoS One*. 2016 Nov 28; 11(11): e0166897. doi:10.1371/journal.pone.0166897.

Summary: To investigate the clinical characteristics, treatments and prognosis of renal cell carcinoma associated with Xp11.2 translocation/TFE3 gene fusions (Xp11.2 tRCC), the epidemiological features and treatment results of 34 cases of Xp11.2 tRCC, which were diagnosed by immunohistochemistry staining of TFE3 and fluorescence in situ hybridization at our center, were retrospectively reviewed. The 34 patients included 21 females and 13 males aged 3 to 64 years (median age: 27 years). Four patients were children or adolescents (<18 years of age), and 26 patients were young or middle-aged adults (18-45 years). Radical nephrectomy was performed on 25 patients. Laparoscopic nephron-sparing surgery was performed on 9 patients who presented with an isolated mass with a small diameter (<7 cm) and well-defined boundary on computed tomography imaging. Postoperative staging showed that 25 cases (73.53%) were at stage I/II, while 9 cases (26.47%) were at stage III/IV. All stage I/II patients received a favorable prognosis with a three-year overall survival rate of 100%, including the patients who underwent laparoscopic nephron-sparing surgery. With the exception of 2 children, the other 7 stage III/IV patients died or developed recurrence with a median follow-up of 29 months. On univariate analysis, maximum diameter, adjuvant treatment, TNM stage, lymph node metastasis, inferior vena cava tumor thrombosis and tumor boundary were identified as statistically significant factors impacting survival (P<0.05). Multivariate analysis indicated that TNM stage and inferior

(continued on page 140)

Highlighting Key Developments in Clinical and Strategic Thinking From Web-Based Sources

Squibb, Calithera Biosciences Announce Clinical Collaboration to Evaluate Ninvolumab in Combination with CB-839 in Clear Cell RCC

NEW YORK and SOUTH SAN FRANCISCO—A clinical trial collaboration will evaluate nivolumab (Opdivo®) in combination with Calithera's CB-839 in patients with clear cell renal cell carcinoma (ccRCC). CB-839 is an orally administered glutaminase inhibitor currently in Phase 1/2 clinical studies.

Preclinical data suggest that CB-839, designed to target a pathway to starve tumor cells of the key nutrient glutamine, may enhance the effects of checkpoint inhibitors and may also reverse tumor resistance to checkpoint inhibitors by altering the immune-suppressive microenvironment and promoting an anti-tumor immune response. Nivolumab is designed to overcome immune suppression. The companies will explore the potential of combining these two agents with the goal of achieving improved and sustained efficacy in ccRCC patients with cancer that is stable or growing on a PD-1 inhibitor therapy.

"The combination with Opdivo follows our strategy to combine CB-839 with therapies to improve outcomes for RCC patients," said Susan Molineaux, CEO of Calithera Biosciences. "We believe that by blocking glutamine consumption in tumors, and redirecting this key nutrient for cell growth and proliferation to T-cells, CB-839 could enhance the effects of Opdivo. With support from Bristol-Myers Squibb, Calithera is excited to advance this combination into the Phase 2 portion of CX-839-004, our ongoing study in ccRCC patients."

Opdivo currently has regulatory approval in 57 countries including the United States, Japan, and the European Union.

Argos Therapeutics Enters Strategic Research Agreement with Personalis, Inc.

DURHAM, NC—Argos Therapeutics Inc. has entered into a strategic research agreement with Personalis, Inc., a precision medicine company, focused on genomics solutions for immuno-oncology, cancer, and genetic disease. Personalis will serve as the primary genomic analysis service provider to support ongoing research efforts to demonstrate that Argos' lead product candidate, rocapuldencel-T, specifically targets patient-specific neoantigens without the need to identify them first. Argos will utilize the Personalis ACE ImmunoID™ next-generation sequencing (NGS) platform to evaluate tumor samples collected during clinical development of Argos' tumor-specific dendritic cell technology to treat renal cell carcinoma. The analytically validated ACE ImmunoID platform offers the unmatched accuracy through whole exome and transcriptome sequencing for tumor/normal evaluation coupled with leading edge bioinformatics and sample tracking to ensure timely delivery of results including neoantigen identification and tumor mutational burden.

"The Personalis technology is a key component to our efforts to further understand the mechanism of action of our lead product, rocapuldencel-T for the treatment of advanced renal cell cancer. We hope to demonstrate that rocapuldencel-T specifically targets neoantigens found only in the patients' tumors to explain why we observe tumor regression without autoimmunity to the unaffected contralateral kidney," said Dr. Charles Nicolette, chief scientific officer and vice president of research and development for Argos.

Robotic Nephrectomy for Localized RCC On The Rise

SAN ANTONIO—Use of robotic radical nephectomy (RRN) to treat stage 1 renal cell carcinoma (RCC) is on the rise in the United States, investigators reported at the Society of Urologic Oncology 17th annual meeting in San Antoni.

Using the National Cancer Data Base, Matthew Bream, MD, and colleagues at Case Western Reserve University in Cleveland identified 15,756 patients undergoing minimally invasive radical nephrectomy (RN)—either robotic radical nephrectomy (RRN) or laparoscopic RN (LRN)—for localized T1 RCC from 2010 to 2013. During the 4-year study period, 25% of these patients underwent RRN, with the proportion of cases treated with RRN increasing significantly over time from 18% in 2010 to 31% in 2013, Dr Bream's group stated in a poster presentation.

On multivariable analysis, patients treated at academic hospitals had significant 29% higher odds of undergoing RRN compared with those treated at community hospitals, the investigators reported. Patients with tumor size of 4 cm or less and those who underwent retroperitoneal lymph node dissection had significant 25% and 86% higher odds, respectively, of undergoing RRN.The RRN and LRN groups were similar with respect to perioperative quality indicators and conversion to open surgery. "With similar perioperative quality outcomes and increased attention to health care costs, RRN may face greater scrutiny as a surgical option for localized RCC," Dr Bream and his colleagues concluded.

(continued on page 141)

Pivotal CABOSUN Trial Reshapes Treatment Options For Intermediate, Poor-RISK RCC


Robert A. Figlin, MD


Toni Choueiri, MD


Gisela Schwab, MD

This Roundtable discussion focuses on results from CABOSUN, a pivotal clinical trial and how data emerging from it could reshape the treatment landscape in kidney cancer. The moderator is Robert A. Figlin, MD, Editor-in-Chief of the Kidney Cancer Journal. *The discussion includes Toni Choueiri, MD, Principal Investigator for METEOR, and Gisela Schwab, MD, Chief Medical Officer of Exelixis, a biopharmaceutical company focused on developing and commercializing small molecule therapies with the potential to improve the treatment of cancer. The company is the developer of cabozantinib.*

Dr Figlin: The pivotal trial has demonstrated both a PFS and survival advantage in the second line treatment of RCCa. How should the practicing oncologist use these data to determine whom to offer this treatment?

Dr Choueiri: The pivotal phase 3 study METEOR demonstrated significant improvements in overall survival, progression-free survival and objective response rate with cabozantinib as compared to everolimus. The results were clinically meaningful and consistently favored (**Table**) cabozantinib across multiple prespecified and post-hoc sub-group analyses indicating benefit across all patient subgroups regardless of prognostic risk, extent of disease, prior VEGFR TKI regimen, MET status, or age. The safety profile was generally similar to that observed with other TKIs which target VEGFR. We presented and published the results of METEOR 2015 and 2016[1,2].

Dr Schwab: These results led to regulatory approval of Cabometyx (cabozantinib) by the FDA in April 2016 and by the EMA in September 2016. Cabometyx is a new standard of care for RCC patients after prior anti-angiogenic therapy and can be offered to this patient population.

Dr Figlin: With other recently approved agents in the second line setting of RCCa (Opdivo, lenvatinib/everolimus) we need to describe how to assist the practicing oncologist in choosing between these recently approved agents in this setting.

Dr Choueiri: Both Cabometyx and Opdivo showed significant improvements in overall survival and response rate in their privotal trials in previously-treated RCC patients. However, Cabometyx demonstrated significant improvements in all three key efficacy endpoints of overall survival, progression-free survival and objective response rate, making it the only agent showing consistent benefit across all three key efficacy endpoints in a large randomized phase 3 study.

Lenvatinib in combination with everolimus was studied in a smaller randomized phase 2 trial in which the combination showed significantly improved PFS and objective response rate, and improved OS compared with everolimus.

All three agents have achieved regulatory approval. However, the strength of evidence for Cabometyx and Opdivo resulted in a preferred NCCN category 1 recommendation. This means that patients and physicians have several treatment options without a clear front-runner, as none of these therapies has been compared in a head-to-head trial.

Dr Figlin: With the CABOSUN data evolving would you describe the study design and results and whether cabozantinib should be a consideration for the upfront treatment in RCCa?

Dr Schwab: CABOSUN is a randomized phase 2 trial comparing cabozantinib and sunitinib in the front-line treatment of patients with intermediate or poor risk RCC. CABOSUN was conducted by the Alliance for Clinical Tri-

Keywords: CABOSUN, cabozantinib, sunitinib, METEOR, VEGF, TKI.

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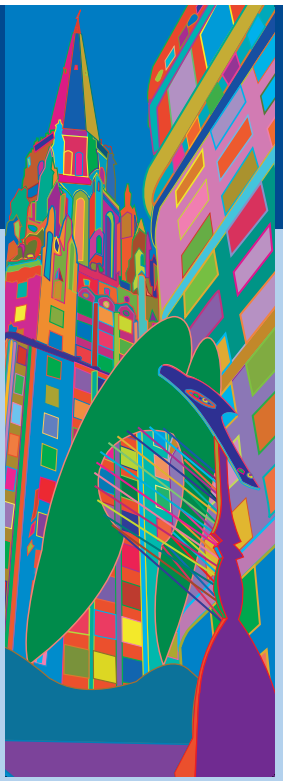

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Table. Summary of METEOR Results

	Cabozantinib (N=330)	Everolimus (N=328)
Median Progression-Free Survival* (mo)	7.4	3.9
95% CI (mo)	6.6, 9.1	3.7, 5.1
PFS Hazard Ratio (95% CI), P value	0.51 (0.41, 0.62), P<0.0001	
Median Overall Survival* (mo)	21.4	16.5
95% CI (mo)	18.7, NE	14.7, 18.8
OS Hazard Ratio (95% CI), P value	0.66 (0.53, 0.83), P=0.0003	
Objective Response Rate by IRRC (%)	17	3
95% CI (%)	13, 22	2, 6
ORR P value	P<0.0001	
Pts with Gr3 or4 AE (%)	71	60
Pts with Dose Reductions (%)	62	25
Treatment Discontinuation for AEâ€ (%)	12	11

*As assessed in the entire study population. Study primary endpoint was PFS assessed in first 375 patients enrolled.
†Not related to disease progression.
IRRC, independent radiological review committee; AE, adverse event.
Choueiri TK et al, *Lancet Oncol*. 2016.

als in Oncology with the sponsorship of NCI-CTEP and under a CRADA between Exelixis and NCI-CTEP. Dr. Choueiri is the principal investigator of the study.

The primary objective of the study was to evaluate whether progression-free survival with cabozantinib would be improved compared to sunitinib. Secondary endpoints included objective response rate, overall survival and safety.

Dr Choueiri: CABOSUN enrolled 157 intermediate or poor risk RCC patients. Patients were stratified by risk group (intermediate vs poor) and presence of bone metastases (yes vs no). 81% of patients were intermediate risk and 19% poor risk; 36% of patients had bone metastases. We presented the results at the 2016 ESMO conference and the data are now published in the *Journal of Clinical Oncology*.[3] CABOSUN met its primary endpoint of significantly improving PFS with cabozantinib as compared with sunitinib: median PFS was 8.2 months with cabozantinib and 5.6 months with sunitinib. The hazard ratio was 0.66 and the one-sided *P* value 0.012. Subgroup analyses by stratification factors including risk group and presence of bone metastases consistently favored cabozantinib. The objective response rate was also significantly higher with cabozantinib compared to sunitinib with 46% vs 18% of patients achieving a confirmed objective response. Reductions in target lesion size were seen in 87% on the cabozantinib arm compared to 44% on the sunitinib arm.

Overall survival results were not mature with a minimum follow-up of 16 months. The median overall survival on cabozantinib was 30.3 months and on sunitinib 21.8 months. The hazard ratio was 0.80 favoring cabozantinib, but the results were not statistically significant. Follow-up is ongoing, and an additional overall survival analysis is planned when the data have further matured. Safety profiles were similar in both treatment arms and the frequency and nature of adverse events was consistent with those previously observed.

CABOSUN is the first trial showing a statistically significant and clinically meaningful benefit for a new agent over the standard of care treatment in this setting, sunitinib. These results indicate that cabozantinib may be a potential (**Figures 1**,**2**) new treatment option for previously untreated patients with intermediate or poor risk RCC.

> "Caboantinib's targets include MET, AXL and VEGFRs. The superiority of cabozantinib over sunitinib observed in CABOSUN may reflect this differentiated target profile of cabozantinib. Further investigation of biomarkers is currently ongoing and may help to clearly define the roles of these targets in the clinical activity of cabozantinib."

Dr Figlin: Recent data have suggested that sunitinib may be helpful in high risk resected disease as an adjuvant therapy. Does this mean that cabozantinib might be a treatment choice in this population if they progress following adjuvant therapy?

Dr Choueiri: The S-TRAC study was also presented at the 2016 ESMO conference and showed improved disease-free survival in high risk RCC patients who received adjuvant treatment with sunitinib compared with placebo.

If sunitinib were adopted as a new treatment option in the adjuvant setting, it is possible that cabozantinib could become a treatment choice after patients progress on adjuvant therapy. In the METEOR trial, cabozantinib showed strong results in the second line setting following first-line sunitinib, and now has demonstrated better outcomes compared to sunitinib in CABOSUN in the first line treatment of intermediate and poor risk RCC patients. Together these data support the use of cabozantinib in the first line after relapse on adjuvant therapy with sunitinib.

These results are important when thinking about future trials which could include combinations of cabozan-

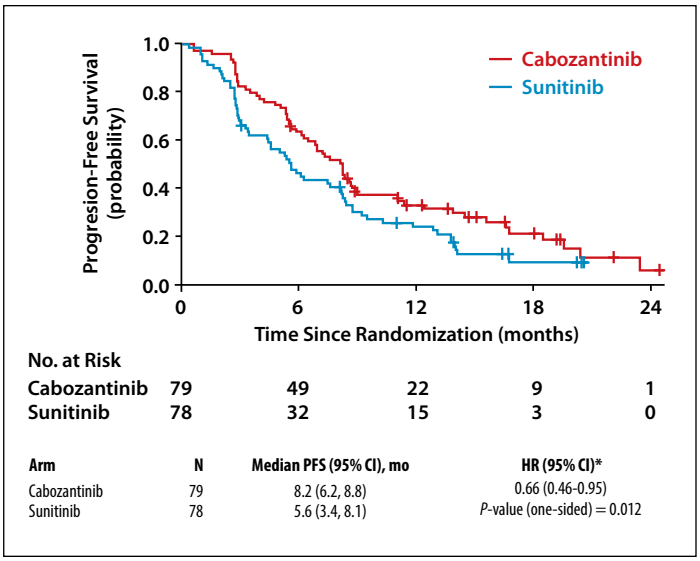

Figure 1. Kaplan-Meier Plot of Progression-Free Survival in the CABOSUN Trial. Best target lesion change from baseline with cabozantinib (left) and sunitinib (right). Three patients in the cabozantinib group and 16 patients in the sunitinib group were not evaluable because they had no postbaseline imaging assessments.

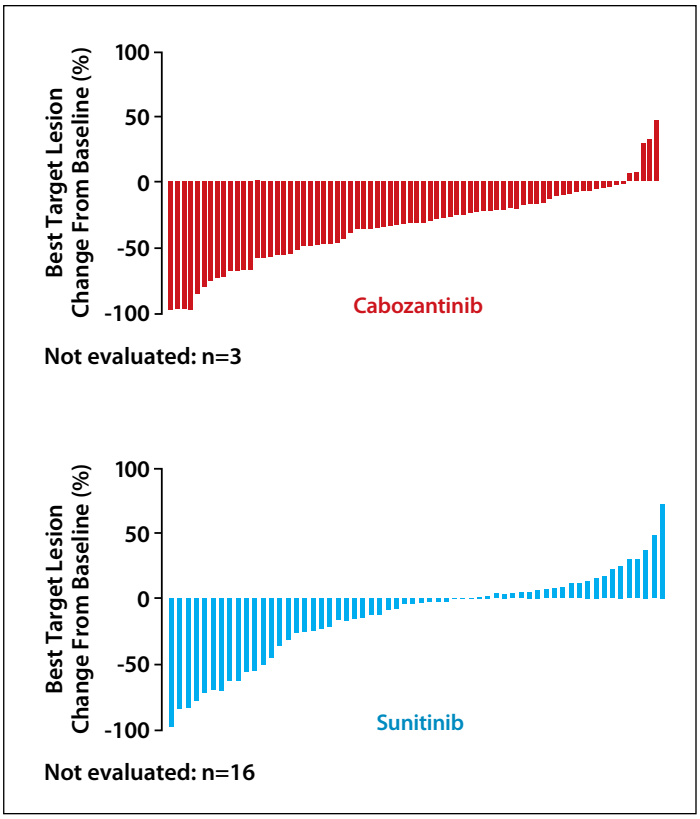

Figure 2. Best Target Lesion Change from Baseline in CABOSUN Best target lesion change from baseline with cabozantinib (left) and sunitinib (right). Three patients in the cabozantinib group and 16 patients in the sunitinib group were not evaluable because they had no postbaseline imaging assessments. Choueiri TK et al. *J Clin Oncol* 2016

tinib and immune checkpoint inhibitors such as nivolumab, as both agents have shown significant single-agent activity in the treatment of RCC.

Dr Figlin: Since cabozantinib targets many pathways, are there any updates on biomarkers that speak to how this agent works and benefits patients?

Dr Choueiri: Caboantinib's targets include MET, AXL and VEGFRs. The superiority of cabozantinib over sunitinib observed in CABOSUN may reflect this differentiated target profile of cabozantinib. Further investigation of biomarkers is currently ongoing and may help to clearly define the roles of these targets in the clinical activity of cabozantinib. However, the role of MET tumor expression was investigated in the METEOR trial and was not found to be predictive of the clinical activity of cabozantinib over everolimus. Additionally, cabozantinib has been shown to have immunomodulatory effects in the tumor microenvironment, supporting the ongoing evaluation of the combination of cabozantinib with immune checkpoint inhibition.

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S-TRAC and Its Implications: Finally, a New Paradigm for Adjuvant Therapy Emerges

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One of the more elusive goals in the treatment of renal cell carcinoma is now within reach based on results from a landmark trial in adjuvant therapy following nephrectomy in locoregional disease. And yet, much investigative work still needs to be done to achieve a long awaited improvement in overall survival.

Two clinical trials, each with similar objectives yet producing distinctly different outcomes, highlight significant variations in disease-free survival with the use of adjuvant sunitinib. These trials help delineate important factors that may underlie the results following this strategy.

Rarely can the results of a trial legitimately be considered a milestone, but the S-TRAC (Sunitinib as Adjuvant Treatment for Patients at High Risk of Recurrence of Renal Cell Carcinoma) qualifies as a landmark study. With results from the S-TRAC trial reported by Ravaud et al, it was clear that a new era might be emerging in renal cell carcinoma (RCC) where previously we thought there was no hope—that of the benefit of adjuvant therapy.[1]

The S-TRAC trial represented the first positive study after many failed adjuvant trials for patients with RCC post nephrectomy. Although this positive trial yielded a cautionary acceptance for sunitinib in clear cell carcinoma only in a homogenously higher-risk patient population, it represents the beginning of a new optimism for adjuvant therapy benefits in kidney cancer.

"The S-TRAC trial represented the first positive study after many failed adjuvant trials for patients with RCC post nephrectomy. Although this positive trial yielded a cautionary acceptance for sunitinib in clear cell carcinoma only in a homogenously higher-risk patient population, it represents the beginning of a new optimism for adjuvant therapy benefits in kidney cancer."

S-TRAC is also significant in at least one other respect: its results stand out compared to a similarly designed trial—ASSURE (Adjuvant Sunitinib or Sorafenib for High-Risk, Non-Metastatic Renal Cell Carcinoma) or ECOG 2805.[2] In this phase 3 trial, involving patients with locally advanced RCC, investigators did not find any treatment advantage for adjuvant therapy with sunitinib or sorafenib over placebo. The most important question arising from a comparison of ASSURE vs S-TRAC is why did patients in S-TRAC respond to the sunitinib regimen while in the ASSURE trial they did not. A comparison of the two trials reveals how differing methodologies, including dosing strategies and patient selection had an impact on the results. Regardless of these differences, the focus needs to be on S-TRAC and how it can reshape the treatment landscape in locoregional RCC. Still a second key question is whether the FDA will approve sunitinib for this indication, thereby offering clinicians a remarkable new option in therapy.

Sunitinib provides this exciting option, given the increase in disease-free survival and the manageable safety profile seen in S-TRAC. The results of this trial could change practice patterns because there is currently no standard treatment in this setting.[1]

Inside S-TRAC and Its Methodology

In this trial, sunitinib was started at a full dose 50 mg for 4 weeks on, 2 weeks off, and was associated with a median duration of disease-free survival of 6.8 years (95% CI, 5.8–NR) in the sunitinib group vs 5.6 years (95% CI, 3.8–6.6) in the placebo group. The hazard ratio was 0.76 (P = .03). At 3 years, 64.9% of the sunitinib group was dis-

Keywords: Adjuvant therapy, S-TRAC, ASSURE, post nephrectomy, sunitinib, disease-free survival, locoregional RCC.

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ease-free vs 59.5% in the placebo group. At 5 years, 59.3% were disease-free in the sunitinib group vs 51.3% in the placebo group. Overall survival data were not yet complete.

Adverse events were responsible for dose reductions in 34.3% of the sunitinib group compared with only 2% of placebo patients. There were more treatment interruptions as well (46.4% vs 13.2%) and more treatment discontinuations (28.1% vs 5.6%). Despite a similar number of serious adverse events, there were significantly more frequent grade 3/4 adverse events in the sunitinib group vs the placebo group (48.4%/15.8% vs 12.1%/3.6%).

The study randomized 615 patients with clear cell RCC to receive sunitinib (n = 309) or placebo (n = 306). Patient characteristics were well balanced between the arms. The median age of patients in the sunitinib arm was 57 years, and most were males (71.8%). Most patients had an ECOG performance score of 0 (73.8%). Overall, 90.6% of those in the sunitinib arm had a stage 3 tumor, with no nodal involvement and no metastasis. Of these patients, 37.2% were considered low-risk (any Fuhrman grade and ECOG score of 0 or Fuhrman grade 1 and ECOG score of ≥1) and 53.4% were high-risk (Fuhrman grade ≥2 and ECOG score of ≥1).

The remainder of the patients had either stage T4 tumors or had locoregional nodal involvement. Sunitinib was administered at 50 mg daily for 4 weeks followed by 2 weeks without treatment. One dose reduction was allowed in the study, to 37.5 mg per day. Overall, more than half of patients (54.2%) were able to maintain treatment with the starting dose of 50 mg per day. The median daily dose was 45.9 mg.

Treatment-emergent AEs were experienced by 99.7% of patients treated with sunitinib versus 88.5% in the placebo arm. Treatment-emergent AEs by investigator assessment occurred in 98.4% of those treated with sunitinib versus 75.7% with placebo. AEs led to discontinuation for 28.1% of patients in the sunitinib arm versus 5.6% of those in the placebo group.

The most common AEs in the sunitinib arm were diarrhea (56.9%), palmar–plantar erythrodysesthesia (50.3%), hypertension (36.9%), fatigue (36.9%), and nausea (34.3%). The most common grade 3/4 AEs were palmar–plantar erythrodysesthesia (16%), neutropenia (8.5%), hypertension (7.8%), and thrombocytopenia (6.2%). The rate of serious adverse events AEs was similar for sunitinib (21.9%) versus placebo (17.1%).

Results from the ASSURE Trial

In the phase 3 ASSURE trial neither sunitinib nor sorafenib (Nexavar) improved outcomes when administered after surgery to patients with locally advanced RCC. The trial enrolled patients with non-clear cell histology (21%), those at intermediate risk (50%), and patients with less than stage 3 disease (34%). Additionally, the starting daily

(continued on page 137)

KCJ INTERVIEW

Inside the Clinical Trials on Adjuvant Therapy and Re-examining Its Risk/Benefit Ratio

This interview was conducted with Allan J. Pantuck, MD, one of the authors of a study recently published in the New England Journal of Medicine, and Alexandra Drakaki, MD, PhD, on the use of adjuvant sunitinib in high-risk renal cell carcinoma after nephrectomy. A leading investigator on numerous clinical trials, Dr Pantuck is Professor of Urology at the UCLA Department of Urology, Los Angeles, California. Dr Pantuck's research programs focus on gene and immune therapies for genitourinary cancer, molecular and genomic characterization of kidney cancer, and nutritional chemoprevention of prostate cancer. Dr. Drakaki is an Assistant Professor of Medicine (Hematolgy/Oncology) and Urology and the Medical Director of the GU Oncology Program at the Institute of Urologic Oncology at UCLA. Dr. Drakaki is the principal investigator of pivotal genitourinary clinical trials. Her research focus is on the role of non-coding RNAs in GU malignancies and identification of novel drugs that will be used from the bench to the bedside.

Q. Please define the importance of adjuvant therapy in kidney cancer and delineate the efforts so far to make progress in this area.

Dr Drakaki: There are a number of major issues. The most important to consider is that an effective adjuvant treatment is one of the "Holy Grails," not just for kidney cancer, but in all of oncology. There are relatively few cancer sites, such as lung, breast, colon or melanoma, where adjuvant therapies have proven to be effective. 16% of all RCC cases are loco-regional at the time of diagnosis, and depending on their clinical and pathologic features, up to 40% of these patients will ultimately relapse and develop metastatic disease after surgery. Investigators have been attempting to find an effective adjuvant therapy in kidney cancer for decades, going all the way back to the time when interleukin-2, interferon and hormonal therapies were considered the primary options of treatment; however none of these therapies, even when effective in the metastatic setting, proved to be effective in preventing relapse after primary treatment.

Q. How would you characterize the latest results from the S-TRAC (Sunitinib Treatment Of Renal Adjuvant Cancer) trial as compared with other data recently published?

(continued on next page)

Dr Pantuck: The fact that we now have an effective strategy as determined by S-TRAC is a landmark in kidney cancer. There have been three large adjuvant studies published just in the last year. One was the ASSURE (Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma) study, one was the ARISER study (Adjuvant RENCAREX® Immunotherapy trial to Study Efficacy in non-metastasized Renal cell carcinoma), and most recently the S-TRAC trial. There is also a fourth, ongoing trial having a similar design in which pazopanib is being used in the adjuvant setting, however the results of this study are still pending. To date, the S-TRAC study represents the only adjuvant study in RCC to have a positive result.

Q. How would you distinguish between the results, particularly with regard to ASSURE and S-TRAC?

Dr Pantuck: There are a number of important distinctions. First, the S-TRAC study was positive and the ASSURE trial was negative. The ASSURE study was similar to S-TRAC in its enrolling patients at high risk for recurrence and placing them on a year of sunitinib (Sutent®). The ASSURE study, however, had three arms—sunitinib, placebo, and sorafenib. Two important differences in these studies were the eligibility criteria and dosing. For example, the S-TRAC study mandated that all subjects have clear cell preponderant histology, while the ASSURE study accepted all RCC subytpes except collecting duct and medullary carcinomas. The ASSURE study also allowed for a greater number of lower risk patients—those who had a lower risk of locoregional recurrence after nephrectomy. These were patients with high grade T1b and any grade T2 tumors. In the S-TRAC trial the population tended to include patients at higher risk for recurrence, which included only high grade T2, T3, T4 and node positive patients.

Secondly, there were differences in the dosing regimens between the two studies. The ASSURE study began at a lower dose of Sunitinib, and allowed dose reductions down to 25 mg./day, while S-TRAC mandated treatment initiation at 50 mg/day and allowed dose reductions only down to 37.5 mg/day, which clearly resulted in differences in exposure to sunitinib between the two studies. These represented several possible reasons why one study would be positive while the other was negative.

Q. How then, would you assess the implications of S-TRAC in terms of its effect, if any, on clinical practice?

Dr Drakaki: This is the most important question. We do not know yet for certain whether the FDA will approve the adjuvant labeling for sunitinib. By granting approval for the drug for this indication, the FDA would be broadening the use of sunitinib to high-risk, non-metastatic, post-nephrectomy patients—basically adjuvant usage. And it would be the first drug approved for the prevention of recurrence in this context. The question is whether clinicians will adopt the use of sunitinib in this setting even if given the labelling approval by the FDA since, in the metastatic setting, the first line-drug of choice for many clinicians is pazopanib over sunitinib due to its better side effect profile

Q. On what basis would clinicians be hesitant to use it as adjuvant therapy?

"We do not know yet for certain whether the FDA will approve the adjuvant labeling for sunitinib. By granting approval for the drug for this indication, the FDA would be broadening the use of sunitinib to high-risk, non-metastatic, post-nephrectomy patients—basically adjuvant usage. And it would be the first drug approved for the prevention of recurrence in this context." — *Dr Drakaki*

Dr Pantuck: There are reasons why they may, at least at first glance, be hesitant to do so. When you look at the data from the ASSURE study and the S-TRAC trial, there were a significant number of patients who discontinued the treatment because of toxicity. Although it should be stated that the safety profile of adjuvant sunitinib in both S-TRAC and ASSURE was acceptable and consistent with the experience in metastatic RCC, we are dealing with a different patient population in the adjuvant setting. These patients have undergone and have recovered from their surgery, and are now presumably feeling fine and have no evidence of disease but merely the risk of cancer recurrence.

Understandably, someone with metastatic disease would be willing to accept a high degree of inconvenience and adverse toxicity and side effects. Metastatic disease makes for a clear and compelling argument to accept the adverse effects. But, on the other hand, if you have no evidence of metastatic disease but only a risk for recurrence disease, your propensity for accepting and being compliant to a toxic regimen may be less. The ideal adjuvant agent would have minimal side effects and have the ability to completely eradicate micrometastatic disease., However sunitinib does have significant side effects, and instead of being cytotoxic, it is a cytostatic anti-angiogenic agent that exerts a treatment effect through preventing growth of new blood vessels. If it only prevents the growth of new blood vessels, what happens after you discontinue the drug after a year? Will tumors grow at that point? If so, will they then be resistant to the effects of sunitinib and other anti-VEGF TKIs? These questions remain unanswered.

Q. What were the results from S-TRAC on overall survival and progression-free survival?

Dr Pantuck: In the S-TRAC trial patients were treated for one year and then followed for five years since last patient enrolled for disease recurrence. The study met its primary endpoint of improving disease-free survival (DFS) as determined by blinded independent central review in patients with renal cell carcinoma (RCC) who are at high risk for recurrence after surgery. The median duration of disease-free survival was 6.8 years in the sunitinib group and 5.6 years with a hazard ratio of 0.76 that was statistically significant (P=0.03). At the time the S-TRAC paper was published, there was no difference in overall survival between sunitinib and placebo, however overall survival data were not mature at the time of data cutoff.

Dr Drakaki: It is possible that clinicians and patients may wait until overall survival data matures before making a decision whether or not to recommend using sunitinib in the adjuvant setting. It is not clear that patients will be willing to take the drug for a year solely in order to delay going back on the same or a similar drug a year later. Because when the disease recurs, many patients will be put back on a VEGF TKI. So the question is,

Q. So which patients are likely to be in the group that will benefit the most from administration of sunitinib according to S-TRAC?

Dr Pantuck: The trial answers this question by breaking the patient population into subgroups. If you were in the highest-risk subgroup—say, those with a T4 tumor or those with positive lymph nodes, there was a two-year rather than a one-year improvement in progression free survival in favor of the sunitinib arm compared to placebo. Thus, patients with the highest risk of recurrence also had the greatest benefit. So these highest risk patients may be the ideal group to utilize sunitinib in the adjuvant setting. They have the greatest risk of recurrence and the greatest benefit from adjuvant treatment after nephrectomy.

Q. Where do we go from here? You are optimistic, but what remains to be elucidated?

Dr Pantuck: The bottom line is that we have achieved a milestone, but it is not by any means the end of the story. We still need to find agents with better tolerability profiles and improved overall survival. We're moving into a new era of adjuvant studies. We have spent the last 5-10 years testing the TKIs and now we're preparing to look at additional agents, including the checkpoint inhibitors and other innovative therapies.

Dr Drakaki: There are currently ongoing trials with PD-1 or PD-L1 inhibitors as well as combination of those with CTLA4 inhibitors in the adjuvant setting. The biggest challenge here will be, especially for the combination studies, the safety profile. From our experience using these drugs in advanced disease and other tumor types, immune checkpoint inhibitors could lead to serious immune mediated side effects that could even potentially be life threatening. We would need to see a significant and meaningful overall survival benefit before subjecting patients who may never have recurrence to a potentially toxic therapy. A lot will be learned from those studies and certainly will change the treatment arena for years to come. I envision that those adjuvant trials with immune checkpoint inhibitors will be positive if they are designed correctly. This will lead to the next question which is "what is going to be the best therapy, VEGF TKIs or immune checkpoint inhibitors in the adjuvant setting?" So I am also optimistic and hopeful that we will continue to make progress in this important field. KCJ

(continued from page 135)

dose of sunitinib was modified from 50 mg per day to 35 mg.[2]

The median DFS was 5.8 years in both the sorafenib and sunitinib arms and 6.0 years in the placebo arm. The 5-year DFS rate was 52.8% in the sorafenib arm, 53.8% in the sunitinib arm, and 55.8% in the placebo arm. In those with clear cell carcinoma, the DFS was 5.6 years with sunitinib, 5.1 years with sorafenib, and 5.7 years with placebo. The 5-year survival rate was 76.9% with sunitinib, 80.7% with sorafenib, and 78.7% with placebo.

Earlier efforts to achieve favorable outcomes with other adjuvant therapies in this setting highlight the challenges involved and the disappointing results. They include the following reports:

Chamie et al conducted a randomized trial of 864 patients, to determine if adjuvant weekly girentuximab could be effective following complete resection of localized, high-risk RCC.[3] There was no difference in disease-free survival between patients receiving girentuximab. Although the drug was well tolerated, results from the ARISER trial are discouraging for the use of this monoclonal antibody. The antibody binds carbonic anhydrase IX, a cell surface glycoprotein ubiquitously expressed in clear cell RCC. Earlier studies showing safety and activity led to the investigation into its use as adjuvant monotherapy.

The ARISER study is one of the more recent attempts at validating an adjuvant approach. The challenge of doing so was apparent even 15 years ago when the Cy-

tokine Working Group found that one course of high-dose bolus IL-2 did not produce clinically meaningful benefit when administered postoperatively to patients with resected high-risk RCC.4 The rationale followed by the Working Group was that IL-2 had produced durable response in patients with metastatic disease and therefore could be investigated in those with locoregional disease.

Results are expected in 2017 from another study—SORCE, a randomized, double blind, trial of sorafenib, given for one or three years, vs placebo for patients at moderate or high-risk of disease recurrence after surgical excision of primary RCC.[5] However, if the messages from ASSURE can be extrapolated, it will be a challenge for SORCE investigators to demonstrate benefit from sorafenib in this group.

What's Next? More Adjuvant Trials

In the wake of results from S-TRAC questions remain on how continuing results and forthcoming studies will address unresolved issues. One of these issues is the use of various endpoints, most importantly, DFS vs overall survival. Disease-free survival is a useful surrogate endpoint, but the results from different studies have been contradictory. It does not necessarily translate to overall survival, which is the gold standard.

There are expectations that additional studies will address these questions. The phase 3 ATLAS trial, for example, is currently assessing adjuvant therapy with axitinib (Inlyta) for patients with high-risk, clear cell RCC. This study enrolled 700 patients.[6] Additionally, the phase 3 PROTECT study is looking at adjuvant pazopanib (Votrient) in patients with intermediate or high-risk, clear cell RCC. This large study includes 1540 patients.[7]

In the past several years there has been a resurgence of interest in cancer immunotherapy. The development of blocking antibodies against the inhibitory programmed death-1 (PD-1) pathway represents a clinical breakthrough in the treatment of solid tumors and these agents have shown great promise in RCC. Currently, new checkpoint inhibitor studies are ongoing to evaluate their role as adjuvant therapy. The efforts are intriguing, particularly because they may be able to offer improved side effect profiles. Genentech is conducting one of these studies and Bristol-Myers Squibb is examining a combination of a CTLA4 and PD1 inhibitor. Combined checkpoint blockade, to date explored with CTLA-4 and PD-1 pathway blocking agents, represents a first step in this new direction.

Conclusion

The pivotal S-TRAC trial has been viewed as a milestone in establishing the benefits of adjuvant sunitinib in patients with locoregional clear cell RCC at high-risk for recurrence after nephrectomy. In contrast to the ASSURE trial, in which no improvement in DFS occurred, S-TRAC is expected to reshape treatment for this subgroup of patients. Distinct patient populations, dose regimens, and trial methods were likely responsible for the different outcomes in the two trials. The safety profile in patients treated with adjuvant sunitinib revealed moderate declines in quality of life while receiving active treatment. It remains for S-TRAC and additional studies to further elucidate advantages of the regimen of sunitinib to determine if an overall survival benefit, not yet demonstrated, can be achieved.

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(continued from page 126)

why we need to address more pathways to improve progression-free survival and overall survival. As we embark on our 15th year of publication, another era in treatment looms.

So much of the progress noted has been achieved within the years of this journal's publication, beginning in 2003. The approvals of checkpoint inhibitors and the hopeful signs generated by the CABOSUN and S-TRAC trials delineated in this issue also suggest more questions raised by Dr Hsieh's slide presented at the recent 15th International Kidney Cancer Symposium. For example, will the new focus on immunotherapy fulfill its promise? When and to what extent will vaccine therapies be able to put their stamp on personalized medicine in kidney cancer?

Perhaps timelines such as this are unintentionally deceptive. By breaking up the advances in treatment into convenient and easily visualized points, timelines seem to suggest that we have proceeded at nearly "warp speed" toward new treatments, some even considered revolutionary until patterns of resistance and the re-emergence of disease prove otherwise. But everyone knows the progress is painstakingly incremental.

Nevertheless, it is exciting to see in graphic form how the strategies have emerged over the years, from the first immunotherapies back in 1992, to the introduction of vascular endothelial growth factor (VEGF) inhibitors, mammalian target of rapamycin (mTOR) inhibitors, the tyrosine kinase inhibitors (TKIs) and the checkpoint or PD-1 inhibitors. Perhaps, the next timeline will even incorporate vaccine approaches still under investigation. As accurate as the timeline is in chronicling the expansion of the spectrum of therapy, it might be considered somewhat deceptive because within it, numerous approaches to sequential and combinatorial uses are not apparent. And these strategies—although not apparent in the timeline—have been a critical part of extending progression-free survival.

As the timeline suggests, we have moved from the "Dark Age" to the "Modern Age," to what Dr Hsieh calls the "Golden Age." We applaud his optimism and hope that the so-called Golden Age will usher in even more innovative therapies with a more favorable prognosis for our patients.

Robert A. Figlin, MD
Editor-in-Chief

(continued from page 128)

vena cava tumor thrombosis were independent prognostic factors ($P<0.05$).
Conclusion: Xp11.2 tRCC is a rare subtype of renal cell carcinoma that mainly occurs in young females. Nephron-sparing surgery was confirmed effective preliminarily in the treatment of small Xp11.2 tRCCs with clear rims. Advanced TNM stage and inferior vena cava tumor thrombosis were associated with poor prognosis.

Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of renal cell carcinoma. Rini BI, McDermott DF, Hammers H, et al. *J Immunotherapy Cancer*. 2016 Nov 15; 4:81.

Summary: Immunotherapy has produced durable clinical benefit in patients with metastatic renal cell cancer (RCC). In the past, patients treated with interferon-alpha (IFN) and interleukin-2 (IL-2) have achieved complete responses, many of which have lasted for multiple decades. More recently, a large number of new agents have been approved for RCC, several of which attack tumor angiogenesis by inhibiting vascular endothelial growth factors (VEGF) and VEGF receptors (VEGFR), as well as tumor metabolism, inhibiting the mammalian target of rapamycin (mTOR). Additionally, a new class of immunotherapy agents, immune checkpoint inhibitors, is emerging and will play a significant role in the treatment of patients with RCC.
Conclusion: The Society for Immunotherapy of Cancer (SITC) convened a Task Force, which met to consider the current role of approved immunotherapy agents in RCC. The Task Force provides guidance to practicing clinicians by developing consensus recommendations that set the stage for future immunotherapeutic developments in RCC.

Renal cancer subtypes: Should we be lumping or splitting for therapeutic decision making? Haake SM, Rathmell WK. *Cancer*. 2016 Nov 14. doi: 10.1002/cncr. 30314.

Summary: The treatment of advanced renal cell carcinoma has posed a challenge for decades, in part because of common themes related to intrinsic resistance to cytotoxic chemotherapy and the obscure biology of these cancer types. Forward movement in the treatment of the renal cell carcinomas thus can be approached in 2 ways: by splitting the tumor types along histologic and molecular features, in the hopes of coupling highly precision-focused therapy on a subset of patients who have disease with the most potential for benefit; or by lumping the various biologies and histologies together, to include the rarer renal cell carcinoma types with the more common types.
Conclusion: The aforementioned former strategy satisfies the desire for customized precision in treatment delivery, whereas the latter strategy allows clinicians to offer a wider therapeutic menu in a set of diseases clinicians are continuing to learn about on a physiologic and molecular level.

Adjuvant Sunitinib in High-Risk Renal-Cell Carcinoma after Nephrectomy. Ravaud A, Motzer RJ, Pandha HS, et al. *N Engl J Med*. 2016 Dec 8;375(23):2246-2254.

Summary: Sunitinib, a vascular endothelial growth factor pathway inhibitor, is an effective treatment for metastatic renal-cell carcinoma. We sought to determine the efficacy and safety of sunitinib in patients with locoregional renal-cell carcinoma at high risk for tumor recurrence after nephrectomy. Methods In this randomized, double-blind, phase 3 trial, we assigned 615 patients with locoregional, high-risk clear-cell renal-cell carcinoma to receive either sunitinib (50 mg per day) or placebo on a 4-weeks-on, 2-weeks-off schedule for 1 year or until disease recurrence, unacceptable toxicity, or consent withdrawal. The primary end point was disease-free survival, according to blinded independent central review. Secondary end points included investigator-assessed disease-free survival, overall survival, and safety. Results The median duration of disease-free survival was 6.8 years (95% confidence interval [CI], 5.8 to not reached) in the sunitinib group and 5.6 years (95% CI, 3.8 to 6.6) in the placebo group (hazard ratio, 0.76; 95% CI, 0.59 to 0.98; $P=0.03$). Overall survival data were not mature at the time of data cutoff. Dose reductions because of adverse events were more frequent in the sunitinib group than in the placebo group (34.3% vs. 2%), as were dose interruptions (46.4% vs. 13.2%) and discontinuations (28.1% vs. 5.6%). Grade 3 or 4 adverse events were more frequent in the sunitinib group (48.4% for grade 3 events and 12.1% for grade 4 events) than in the placebo group (15.8% and 3.6%, respectively). There was a similar incidence of serious adverse events in the two groups (21.9% for sunitinib vs. 17.1% for placebo); no deaths were attributed to toxic effects.
Conclusion: Among patients with locoregional clear-cell renal-cell carcinoma at high risk for tumor recurrence after nephrectomy, the median duration of disease-free survival was significantly longer in the sunitinib group than in the placebo group, at a cost of a higher rate of toxic events. KCJ

(continued from page 129)

Everolimus, CB-839 Combination Active in Advanced RCC

MUNICH—The combination of CB-839, a first-in-class selective inhibitor of glutaminase, and everolimus seems to have disease activity in patients with advanced renal cell carcinoma (RCC), according to the results of a phase I study presented at the 28th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics in Munich, Germany.

"To date, tumors in 93% of patients with clear cell and papillary renal cell cancers have had tumor control from the regimen, with a median time without their cancer growing of 8.5 months," said Funda Meric-Bernstam, MD, of the University of Texas MD Anderson Cancer Center in Houston. "For more than half of these patients their time on this treatment has been longer than the time they remained on their prior treatment, which is considered to be a good sign."CB-839 targets glutaminase, an enzyme involved in the conversion of glutamine to glutamate, which is an important nutrient for cancer cells. Early preclinical studies of CB-839 showed that the drug had broad monotherapy activity in RCC, a disease where glutaminase is highly expressed.

This study included patients with previously treated advanced or metastatic RCC, including clear cell and papillary RCC. All patients had four or fewer previous lines of therapy, an ECOG performance status of 0 or 1, and RECIST-measurable disease. Prior treatment with mTOR inhibitors or a checkpoint inhibitor was allowed. The median number of prior therapies was two. The patients were assigned to escalating doses of CB-839 between 400 and 800 mg twice daily combined with a fixed dose of 10-mg everolimus. Disease assessment was performed every 8 weeks.According to Dr Meric-Bernstam, out of 15 patients with clear cell and papillary RCC who have received the drug combination, 93% had their tumor controlled by the regimen. One patient experienced a partial response, with a 30% decrease in tumor size; an additional 13 patients have stable disease. One patient had progressive disease.

Overall, the combination treatment was well tolerated. The researchers observed only one dose-limiting toxicity, a grade 3 rash that occurred at the 400-mg dose. No grade 4 or 5 adverse events occurred, and any grade 3 events were consistent with late-stage cancer or everolimus toxicity, according to the study abstract."These results suggest that CB-839 is a very tolerable drug with significant potential in combination therapy for kidney cancer patients," Dr Meric-Bernstam concluded.

Extensive RCC Agenda Scheduled for GU ASCO Meeting

ORLANDO—The 2017 Genitourinary (GU) Cancers Symposium is scheduled for February 16-18 at Rosen Shingle Creek in Orlando. In educational sessions, expert faculty will offer a multidisciplinary perspective on new research and its clinical application with an emphasis on value in cancer care across the spectrum of GU cancers. Oral abstract presentations and poster sessions will highlight the latest, cutting-edge science, and keynote lectures from internationally renowned speakers will address the most clinically relevant research in the field of GU oncology. The 2017 Symposium will feature extended question-and-anperiods for more robust audience participation, interactive case discussions, and ample time for networking with faculty members and fellow attendees.

HIF-2 Inhibitors Challenge Standard of Care in Animal Model

HIF-2 inhibitors may be more effective and better tolerated than the standard of care sunitinib in treating kidney cancer, researchers with the Kidney Cancer Program at Harold C. Simmons Comprehensive Cancer Center have found. HIF-2 inhibitors, which grew out of research begun more than 20 years ago at UT Southwestern Medical Center, work by interfering with processes that fuel the growth of cells.

Investigators conducted a pre-clinical trial in mice transplanted with kidney cancer from over 20 patients and showed that the HIF-2 inhibitor PT2399 controlled cancer in half of the tumors, according to a study published in the journal *Nature*.

"This is a completely new treatment for kidney cancer. We want to make HIF-2 inhibitors available to patients and are currently carrying out clinical trials," said Dr James Brugarolas, Director of the Kidney Cancer Program, who is leading an $11 million SPORE grant from the National Cancer Institute seeking to translate new discoveries into novel therapies for kidney cancer patients. Part of the SPORE grant, one of just two directly related to kidney cancer in the nation, is focused on further researching HIF-2 inhibitors. HIFs or hypoxia-inducible factors, like HIF-2, allow the body's cells to adjust to low-oxygen environments. HIFs activate programs that promote the development of blood vessels, facilitate oxygen delivery and promote efficient nutrient utilization. Kidney cancer cells hijack the same system to fuel their growth. KCJ

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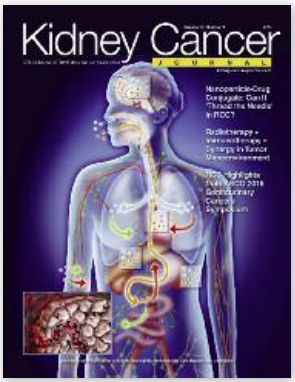

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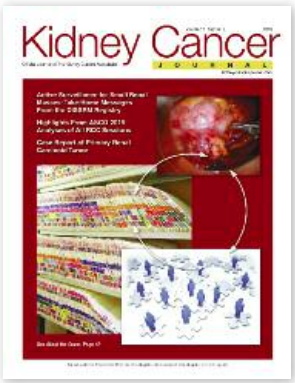

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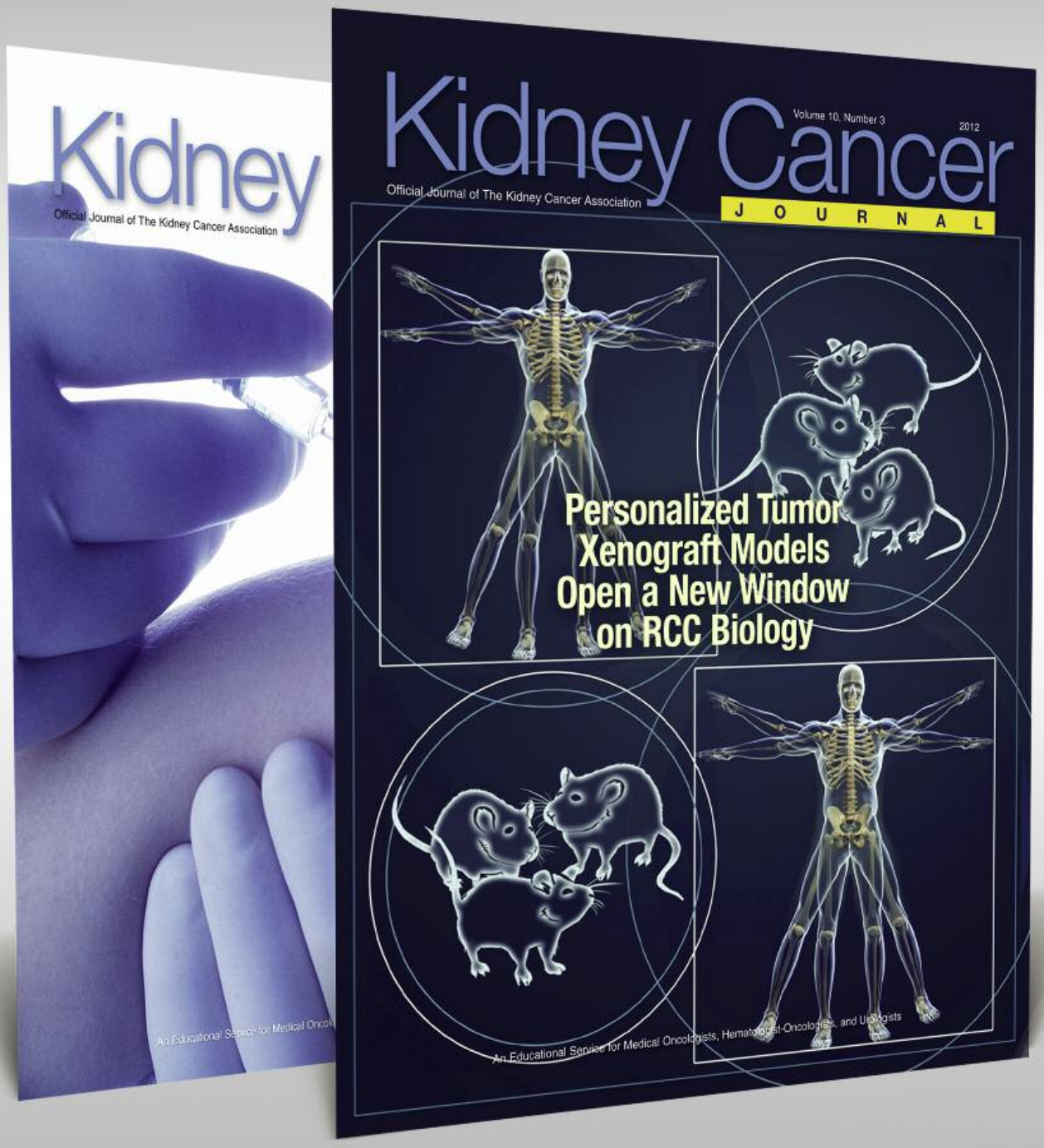

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