Volume 13, Number 2 2015

Kidney Cancer JOURNAL

Official Journal of The Kidney Cancer Association

kidney-cancer-journal.com

ASCO 2015 Highlights: Analysis and Impact

Surveillance After Surgery for mRCC: What Duration Is Optimal?

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

About the Cover
Regardless of whether it is called watchful waiting or active surveillance, the CT scan suggests the need for appropriate followup to detect recurrences of metastatic renal cell carcinoma. Image is of a biopsy of a cancer of the right kidney, visualized by abdominal CT scan. Protocols for use of CT and related imaging studies are evolving after new findings suggest extent to which recurrent tumors may not be detected after various durations of surveillance. (BSIP/Science Source. Copyright © 2015 Photo Researchers, Inc. All Rights Reserved.)

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KCJ GUEST EDITOR'S MEMO

Following the Trail of "Stepping Stones" Left by 2015 ASCO Sessions Points Toward That Elusive "Milestone" in Therapy


Toni Choueiri, MD

Each meeting of the American Society of Clinical Oncology (ASCO) serves as a touchstone for future directions, at least for a year until the next Scientific Sessions present new data on the march toward a cure. The 2015 sessions were no exception, giving us yet another opportunity to view progress through the prism of updated results. Optimization of targeted agents and novel immune checkpoint blockers remain a large focus for all of us engaged in the management of renal cell carcinoma (RCC). The new results from the meeting provide more important insights on this approach to treatment and determining which patients are likely to benefit, based on biomarker findings.

Overall, however, to what extent will the findings presented at ASCO translate into clinical practice? Although there were no "milestones" reached at this meeting—a term often used erroneously by the consumer media —there were many presentations that could be considered "stepping stones" to the major advances in therapy providers are anticipating. For example, there were encouraging results from a phase 2 three-arm study of lenvatinib and everolimus. Lenvatinib is a VEGFR1 TKI inhibitor, and it also inhibits FGFR1 and PDGFR- , RET, and KIT TKI. About 50 patients were in each arm, and progression-free survival with the combination of lenvatinib and everolimus seemed to be significantly prolonged; it was 14.6 months for the combination, 7.4 months with lenvatinib alone, and 5.5 months with everolimus alone. We look forward to seeing a phase 3 trial that will definitely provide additional information.

The role of immune checkpoint inhibitors targeting the PD-1/PD-L1 pathway has been of special interest. Our group presented some interesting prospective biomarker analysis regarding the use of nivolumab in metastatic RCC. Our data suggest provide potential insights into what biomarker might predict response to immune checkpoint inhibitors and why potentially a combination of two immune checkpoint blockers might be better than one Other studies like RECORD-4 discussed the clinical benefit of everolimus post-TKIs or cytokines.

These results offer just a tantalizing preview of what the report in this issue of the *Kidney Cancer Journal* covers. Please see this report for essential information on a broad spectrum of topics related to this year's ASCO meeting. Although information from the ASCO sessions will serve as a

(continued on page 37)

INLYTA® (axitinib)
for the treatment of advanced RCC after failure of one prior systemic therapy

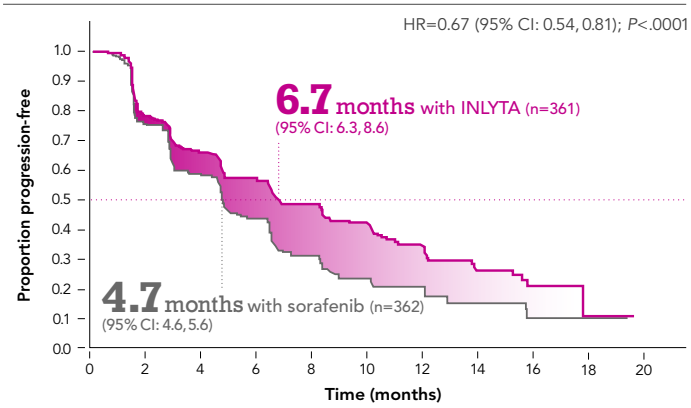
Choose a 2nd-line **treatment** with 2nd-line **evidence**

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

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

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

Primary endpoint: progression-free survival (PFS)



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

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

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

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

Important Safety Information

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

Please see brief summary on the following pages.

Inlyta®
axitinib 1mg and 5mg tablets

INLYTA® (AXITINIB) TABLETS FOR ORAL ADMINISTRATION

Initial U.S. Approval: 2012

Brief Summary of Prescribing Information

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

DOSAGE AND ADMINISTRATION

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

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

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

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

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

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

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

DOSAGE FORMS AND STRENGTHS

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

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

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DRUG INTERACTIONS

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

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

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

USE IN SPECIFIC POPULATIONS

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

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

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

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

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

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

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

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

No dosage adjustment is required in elderly patients.

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

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

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

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

OVERDOSAGE

There is no specific treatment for INLYTA overdose.

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

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

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

NONCLINICAL TOXICOLOGY

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

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

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

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

PATIENT COUNSELING INFORMATION

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

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

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

Rx only August 2014

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

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

Kidney Cancer Journal Author Guidelines

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

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

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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.

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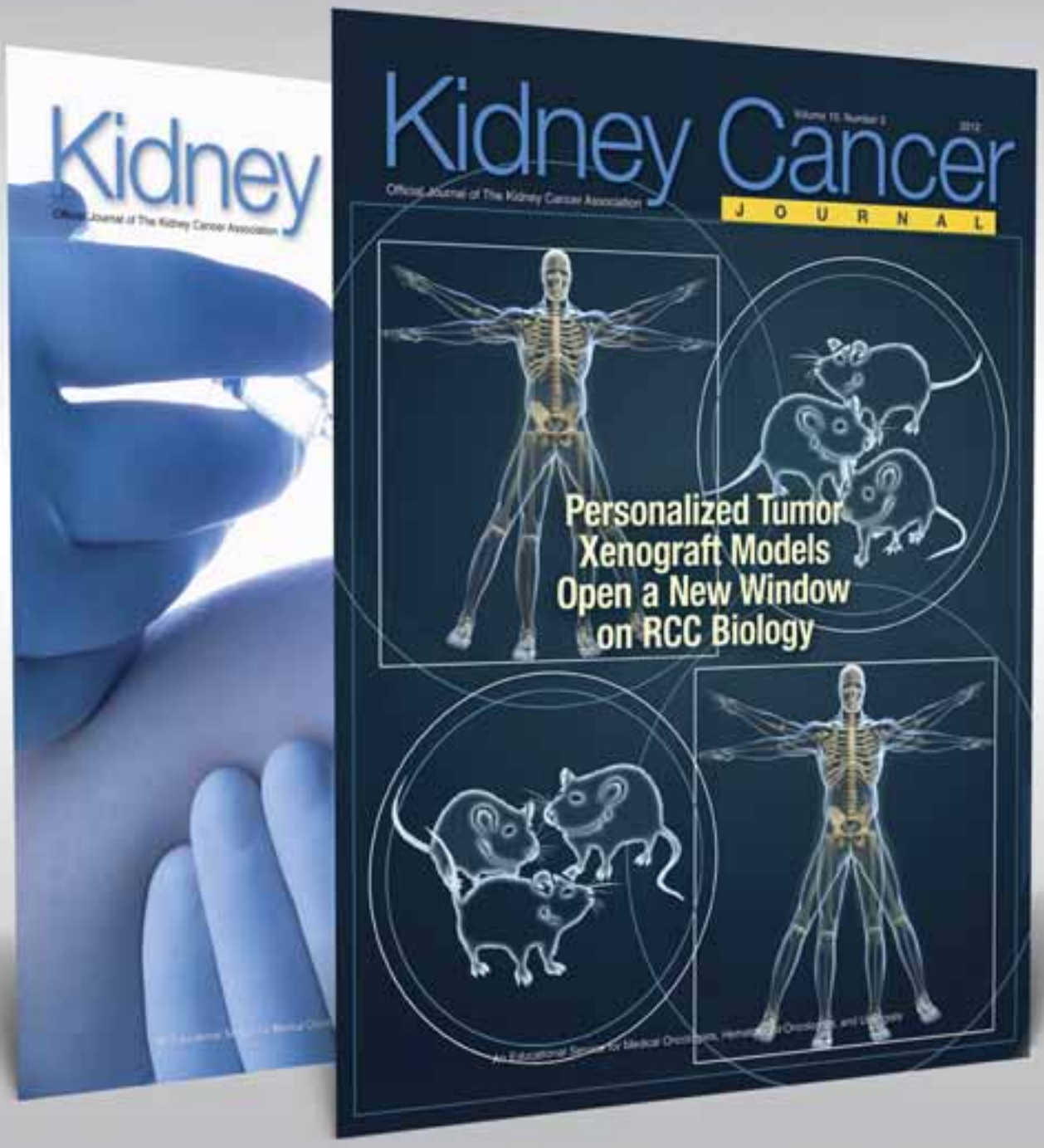

Essential Peer-Reviewed Reading in Kidney Cancer

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

Phase 2 trial of sunitinib and gemcitabine in patients with sarcomatoid and/or poor-risk metastatic renal cell carcinoma. Michaelson MD, McKay RR, Werner L, et al. *Cancer.* 2015 Jun 8. doi: 10.1002/cncr.29503. [Epub ahead of print]

Summary: No standard treatment exists for patients with sarcomatoid renal cell carcinoma (RCC), and treatment options for patients with poor-risk disease are of limited benefit. The objective of this study was to investigate the efficacy of antiangiogenic therapy in combination with cytotoxic chemotherapy in clinically aggressive RCC. This was a phase 2, single-arm trial of sunitinib and gemcitabine in patients with sarcomatoid or poor-risk RCC. The primary endpoint was the objective response rate (ORR). Secondary endpoints included the time to progression (TTP), overall survival (OS), safety, and biomarker correlatives. Overall, 39 patients had sarcomatoid RCC, and 33 had poor-risk RCC. The ORR was 26% for patients with sarcomatoid RCC and 24% for patients with poor-risk RCC. The median TTP and OS for patients with sarcomatoid RCC were 5 and 10 months, respectively. For patients with poor-risk disease, the median TTP and OS were 5.5 and 15 months, respectively. Patients whose tumors had >10% sarcomatoid histology had a higher clinical benefit rate (ORR plus stable disease) than those with ≤10% sarcomatoid histology ($P = .04$). The most common grade 3 or higher treatment-related adverse events included neutropenia (n = 20), anemia (n = 10), and fatigue (n = 7).

Conclusion: These results suggest that antiangiogenic therapy and cytotoxic chemotherapy are an active and well-tolerated combination for patients with aggressive RCC. The combination may be more efficacious than either therapy alone and is currently under further investigation.

Survival, Durable Response, and Long-Term Safety in Patients With Previously Treated Advanced Renal Cell Carcinoma Receiving Nivolumab. McDermott DF, Drake CG, Sznol M, et al. *J Clin Oncol.* 2015 Jun 20;33(18):2013-20. doi: 10.1200/JCO.2014.58.1041. Epub 2015 Mar 30.

Summary: Blockade of the programmed death-1 inhibitory cell-surface molecule on immune cells using the fully human immunoglobulin G4 antibody nivolumab mediates tumor regression in a portion of patients with advanced treatment-refractory solid tumors. This is a report on clinical activity, survival, and long-term safety in patients with advanced RCC treated with nivolumab in a phase I study with expansion cohorts. A total of 34 patients with previously treated advanced RCC, enrolled between 2008 and 2012, received intravenous nivolumab (1 or 10 mg/kg) in an outpatient setting once every two weeks for up to 96 weeks and were observed for survival and duration of response after treatment discontinuation. Ten patients (29%) achieved objective responses (according to RECIST [version 1.0]), with median response duration of 12.9 months; nine additional patients (27%) demonstrated stable disease lasting > 24 weeks. Three of 5 patients who stopped treatment while in response continued to respond for ≥ 45 weeks. Median overall survival in all patients (71% with two to five prior systemic therapies) was 22.4 months; 1-, 2-, and 3-year survival rates were 71%, 48%, and 44%, respectively. Grade 3 to 4 treatment-related adverse events occurred in 18% of patients; all were reversible.

Conclusion: Patients with advanced treatment-refractory RCC treated with nivolumab demonstrated durable responses that in some responders persisted after drug discontinuation. Overall survival is encouraging, and toxicities were generally manageable. Ongoing randomized clinical trials will further assess the impact of nivolumab on overall survival in patients with advanced RCC.

Angiotensin system inhibitors and survival outcomes in patients with metastatic renal cell carcinoma. McKay RR, Rodriguez GE, Lin X, et al. *Clin Cancer Res.* 2015 Jun 1;21(11):2471-9. doi: 10.1158/1078-0432.CCR-14-2332. Epub 2015 Feb 27.

Summary: The renin-angiotensin system may play a role in carcinogenesis. The purpose of this study was to evaluate the impact of angiotensin system inhibitors (ASI) on outcomes in metastatic (mRCC) patients treated in the targeted therapy era. This is a pooled analysis of mRCC patients treated on phase 2 and 3 clinical trials. A total of 4,736 patients were included, of whom 1,487 received ASIs and 783 received other antihypertensive agents. Overall, ASI users demonstrated improved overall survival (OS) compared with users of other antihypertensive agents (adjusted HR, 0.838, $P = 0.0105$, 26.68 vs. 18.07 months) and individuals receiving no antihypertensive therapy (adjusted HR, 0.810, $P = 0.0026$, 26.68 vs. 16.72 months). When stratified by therapy type, a benefit in OS was demonstrated in ASI users compared with nonusers in individuals receiving VEGF therapy (adjusted HR, 0.737, $P < 0.0001$, 31.12 vs. 21.94 months) but not temsirolimus or IFN . An in vitro cell viability assay demonstrated that sunitinib in combination with an ASI significantly decreased RCC cell viability compared with control at physiologically relevant doses. This effect was not observed with either agent alone or with other non-ASI antihypertensives or temsirolimus.

Conclusion: In the largest analysis to date, this study demonstrated that ASI use improved survival in mRCC patients treated in the targeted therapy era. Further studies are warranted to investigate the mechanism underlying this interaction and verify our observations to inform clinical practice.

(continued on page 41)

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

Pivotal Phase 3 Nivolumab mRCC Trial Stopped Early After Superior Overall Survival Advantage

PRINCETON, NJ— An open-label, randomized Phase 3 study evaluating Opdivo (nivolumab) vs everolimus in previously treated patients with advanced or metastatic renal cell carcinoma (RCC) was stopped early because an assessment conducted by the independent Data Monitoring Committee (DMC) concluded that the study met its endpoint. The study demonstrated superior overall survival in patients receiving nivolumab compared to the control arm.

"The results of CheckMate -025 mark the first time an Immuno-Oncology agent has demonstrated a survival advantage in advanced renal cell carcinoma, a patient group that currently has limited treatment options," said Michael Giordano, senior vice president, Head of Development, Oncology, Bristol-Myers Squibb. "Through our *Opdivo* clinical development program, we aim to redefine treatment expectations for patients with advanced RCC by providing improved survival."

CheckMate -025 investigators are being informed of the decision to stop the comparative portion of the trial. Bristol-Myers Squibb is working to ensure that eligible patients will be informed of the opportunity to continue or start treatment with nivolumab in an open-label extension as part of the company's commitment to providing patient access to nivolumab and characterizing long-term survival. The company will complete a full evaluation of the final CheckMate -025 data and work with investigators on the future presentation and publication of the results.

CheckMate -025 is a Phase 3, open-label, randomized study of nivolumab vs everolimus in previously-treated patients with advanced or metastatic clear-cell renal cell carcinoma. The trial randomized 821 patients to receive either nivolumab 3 mg/kg intravenously every two weeks or everolimus 10 mg tablets by mouth daily until documented disease progression or unacceptable toxicity. The primary endpoint is overall survival. Secondary endpoints include objective response rate and progression-free survival.

Argos Completes Patient Enrollment in Pivotal Phase 3 ADAPT Clinical Trial of AGS-003, a Personalized Immunotherapy

DURHAM, NC —Argos Therapeutics Inc., an immuno-oncology company focused on development and commercialization of fully personalized immunotherapies for the treatment of cancer, has announced the pivotal Phase 3 ADAPT clinical trial of AGS-003 in combination with standard targeted therapy for the treatment of metastatic renal cell carcinoma (mRCC) has reached its enrollment goal of at least 450 randomized patients.

"Strong partnerships and coordination across our global study base to identify eligible patients and collect tumor samples have led to successful enrollment for the largest clinical trial ever conducted in patients with newly diagnosed, unfavorable risk, synchronous metastatic RCC," said ADAPT trial co-principal investigator and lead medical oncologist Robert Figlin, MD, the Steven Spielberg Family Chair in Hematology Oncology and Professor of Medicine and Biomedical Sciences at the Cedars-Sinai Samuel Oschin Comprehensive Cancer Institute. "With enough patients screened with successful tumor collection to meet and exceed our target of 450 randomized patients, we look forward to shifting our full attention to the treatment phase of the study and expected data readouts in 2016."

AGS-003 is an autologous dendritic-cell based immunotherapy designed to induce a memory T-cell response specific to each patient's unique tumor antigens. It is produced using a small sample from a patient's own tumor and dendritic cells derived from a leukapheresis procedure. In an open-label Phase 2 study, treatment with AGS-003 plus sunitinib yielded a median overall survival of more than 30 months in newly diagnosed, unfavorable risk mRCC patients.

"By concluding enrollment in the ADAPT trial, we have reached an exciting milestone by demonstrating the ability to rapidly screen and collect tumor samples for more than 1,000 newly diagnosed metastatic RCC patients over the course of approximately two years," said ADAPT trial co-principal investigator and lead urologic oncologist Christopher Wood, MD, Professor of Urology and Deputy Chairman of the Department of Urology, Division of Surgery at the University of Texas MD Anderson Cancer Center. "This would not have been possible without a strong multidisciplinary collaboration among urologists and oncologists, which positions us well to advance our evaluation of AGS-003 in addition to standard treatment through trial completion."

(continued on page 42)

Scientific Sessions Usher in Essential and New Information on a Broad Spectrum of Topics from Biomarkers to Advances in Therapy on Kidney Cancer

Marc R. Matrana, MD, MS
Ochsner Cancer Institute
New Orleans, Louisiana

Stu Chapman
Executive Editor
Kidney Cancer Journal

New targets, potential pathways, data on combination therapies and new information on surgical options were explored in the scientific sessions of this meeting. Overall, the meeting offered a definitive snapshot of where the management of renal cell carcinoma (RCC) stands in 2015. From updates of pivotal trials to explorations of novel and innovative treatments, the sessions, abstracts and posters offer critical information for providers engaged in the treatment of RCC. This report highlights the key findings related to new directions of investigative work in this field.

The cancer-fighting world convened in Chicago for the Scientific Sessions of the American Society of Clinical Oncology (ASCO), a massive annual meeting, attracting more than 30,000 attendees. Several major studies of RCC were discussed and debated.

New Combination Therapy Shows Promising Results

Robert Motzer, MD, presented the results of a randomized phase 2, three-arm trial of the dual VEGF/FGFR-inhibitor lenvatinib vs everolimus vs the combination of lenvatinib vatinib and everolimus in patients with metastatic renal cell carcinoma (RCC) following progression after one prior VEGF-targeted therapy (**Figure 1**). The combination of lenvatinib and everolimus resulted in a median progression-free survival (PFS) of 14.6 months compared to 7.4 months with lenvatinib alone and 5.5 months for single agent everolimus. The combination was also associated with a robust overall response rate of 22% (compared to 14% and 3% in the lenvatinib and everolimus arms, respectively). The median duration of response was longest in the combination group at 13.1 months (compared to 7.5 months with single agent lenvatinib and 8.5 in the everolimus group).

An updated overall survival analysis comparing the combination to single agent everolimus reached statistical significance with a HR of 0.51 (95% CI 0.30–0.88; P = 0.024). The combination was associated with more adverse events, most commonly diarrhea, with 20% having grade 3 or greater diarrhea. A phase 3 randomized trial of this intriguing combination in metastatic RCC is planned.

Targeting ENPP3, A Potential Pathway in Refractory, Metastatic RCC

John A. Thompson. MD, presented the results of a phase 1 study of anti-ENPP antibody drug conjugates in refractory metastatic RCC. ENPP3 is expressed in greater than 90% of clear cell and 70% of papillary RCCs and represents a potential target in treating these two diseases. AGS-16M8F and AGS-16C3F are fully human IgG2k monoclonal antibodies conjugated to microtubule disrupting agent MMAF via a plasma-stable linker, which bind to ENPP3.

Thompson explained that two phase 1 studies were conducted sequentially to test these two agents. 26 patients were treated on the AGS-16M8F study and 34 were treated with AGS-16C3F (**Table 1**). In the 16M8F study, the maximum tolerated dose was not reached, but 3 of 8 subjects at 4.8 mg/kg discontinued for ocular toxicity, most commonly reversible keratopathy. In the AGS-16C3F study, the initial dose of 4.8 mg/kg exceeded maximum tolerated dose. Ocular toxicities were also observed with this agent. This led to a successive de-escalation to 3.6, 2.7, and 1.8 mg/kg. AGS-16C3F was well tolerated at 1.8 mg/kg and showed a median disease control of 23+ weeks and durable partial response in 2 of 10 of clear cell patients and 1 of 3 papillary cases. A phase II study

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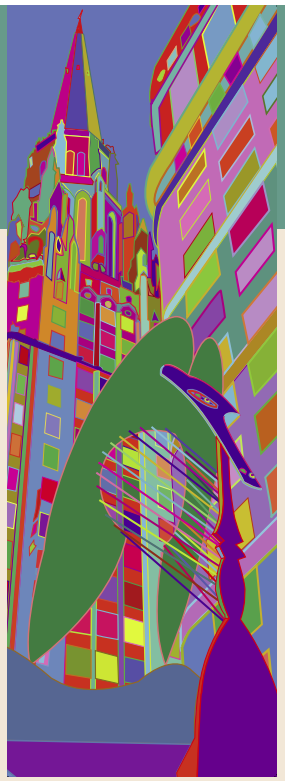

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is plan-ned with AGS-16C3F at 1.8 mg/kg.

Updating The ASSURE Trial On Sunitinib and Sorafenib

Although the results of the adjuvant ASSURE trial (E2805: Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma, an ECOG-ACRIN-led, NCTN Phase 3 Trial), were presented at the Genitourinary Symposium, an updated analysis was presented at this year's ASCO meeting.

The study randomized patients with fully resected RCC to receive 1 year of sorafenib, 1 year of sunitinib, or 1 year of placebo. As previously presented, median disease-free survival was 5.8 years in both the sorafenib and sunitinib groups and 6.0 years in the placebo group, a difference that was not statistically significant. There was no difference in overall survival at 5 years. A large number of patients on trial required dose medications due to toxicity and many were unable to complete a full year of therapy— this led to an amendment to the dosing scheme. Post-hoc analysis revealed that there was no difference in outcome between patients who received more than 6 months of therapy as compared to those who received 3-6 months or less than 3 months of therapy.

Women showed a trend towards better outcomes overall as compared to men, especially those women who received placebo. The authors concluded that adjuvant sorafenib or sunitinib should not be given to patients following full resection of locally advanced kidney cancer.

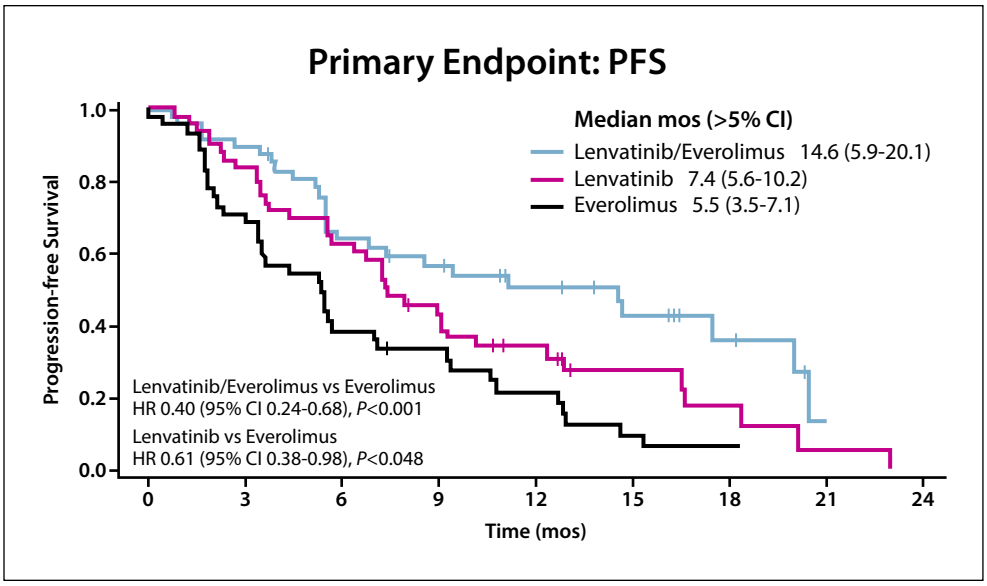

Figure 1. The combination of lenvatinib and everolimus resulted in a median progression-free survival (PFS) of 14.6 months compared to 7.4 months with lenvatinib alone and 5.5 months for single agent everolimus.

ASPEN Trial Yields Final Results on Everolimus vs Sunitinib in Non-clear Cell RCC

The final clinical results of the ASPEN trial (Randomized phase II international trial of everolimus vs. sunitinib in patients with metastatic non-clear cell renal cell carcinoma) were discussed. This multinational trial represents the largest randomized trial to date in non-clear cell metastatic RCC. The trial randomized patients with metastatic non-clear cell to receive either everolimus or suntinib; 108 patients were randomized, and median PFS in the suntinib group was 8.3 months compared to 5.6 months in the everolimus group. This met the pre-defined criteria for statistical significance (**Figure 2**).

Subgroup analysis revealed that those with MSKCC good risk disease benefited most from VEGF-targeted therapy, while those with poor-risk disease trended towards better outcomes with the mTOR inhibitor. Papillary and unclassified RCC seemed to benefit more from sunitinib, while chromophobe trended slightly towards better outcomes with everolimus. The study confirmed the MSKCC criteria in non-clear cell RCC as risk stratification groups were associated with expected outcomes. Patients with chromophobe histology tended to do better than those with other types of non-clear cell RCC.

RECORD-4 Confirms Everolimus as Second-line Therapy After TKI Failure

Bernard Escudier, MD discussed Robert Motzer's RECORD-4 trial, a multi-center phase 2 study of second-line everolimus in patients with metastatic RCC. The results largely confirmed that efficacy of everolimus in the second-line setting following failure of a first-line TKI.

Dr Escudier also discussed an abstract that showed that activating genomic mutations in the mTOR pathway predict responses to mTOR inhibitors in patients with metastatic RCC. Andre Fay, MD, and colleagues found that mutations in *MTOR*, *TSC1* or *TSC2* were more common in patients with clinical benefit from everolimus or temsirolimus. Specifically, mutations in those 3 genes were associated with partial or complete response to mTOR inhibitors. They further noted that neither PTEN nor PIK3CA mutations showed any association with response.

Biomarker Study Enhances The Potential Benefit of Nivolumab

Toni Choueiri, MD, presented an abstract entitled "Immunomodulatory activity of nivolumab in metastatic renal cell carcinoma (mRCC): Association of biomarkers with clinical outcomes." This prospective biomarker study in patients with metastatic RCC treated with the programmed death-1 (PD-1) inhibitor antibody nivolumab assessed baseline and changes in serum chemokines, tumor T cell infiltrates, gene expression, T cell repertoire, and other biomarkers potentially associated with clinical outcomes (**Table 2**).

The authors concluded that "the association of im-

Table 1. Safety results of a phase1 study of anti-ENPP antibody drug conjugates in refractory metastatic RCC.

	AGS-16M8F	AGS-16C3F	AGS-16C3F
	All Doses	All Doses	1.8 mg/kg
N	26	34	13
Median prior systemic therapies	3 (0-8)	3 (0-9)	3 (2-7)
Relevant AEs (All / ≥ grade 3)			
OT	8 / 1	29 / 10	12 / 2
TCP	8 / 3	11 / 6	2 / 1
Fatigue/asthenia	12 / 1	26 / 6	12 / 3
Median wks on therapy	12 (1-80)	9 (1-66)	18 (9-48+)
ORR	1 PR, 9 SD	3 PR, 17 SD	3 PR, 9 SD
Median Disease Control (PR+SD, wks)	21 (12-80)	18 (6 - 66)	23+ (9- 48+)

mune markers at baseline with subsequent tumor burden response suggests that infiltrating immune activating cells may mediate response to nivolumab in metastatic RCC patients. Consistent with the randomized phase 2 study of nivolumab in mRCC, OS appears longer in PD-L1+ patients but promising in both PD-L1+ and PD-L1– patients, especially when treatment-naïve."

Meta-analysis Reveals More About Role of Metastasectomy in Subgroups of Patients and Its Benefits

Axel Bex, MD, discussed the evolving role of metastasectomy in RCC. He noted that retrospective trials have showed 5-year survival rates following complete metastasectomies approaching 70%. It appears that removing multiple sites of metastases also appears to prolong survival in retrospective analyses. Dr Bex and his colleagues conducted a meta-analysis of retrospective studies of metastasectomy and found a definite trend that favored surgical removal of all tumor sites, but he acknowledged inherent biases in these studies.

Principally, patients with aggressive disease typically never have the opportunity to be considered for metastasectomy, while those patients who are offered surgery tend to have low metastatic volume, good performance status, and overall favorable tumor biology with relatively indolent disease. It does appear that metastasectomy results in significant delay in targeted therapy and long term cure in some cases.

Selecting the best patients for metastasectomy remains crucial to improve outcomes. To this end, predictive scores, such as the Leuven-Undine metastasectomy score, have been developed, but these models largely rely on data from the pre-targeted therapy era.

Local therapies to obliterate oligometastatic disease, such as focused radiation therapy, may also offer benefit to patients. Using targeted therapy to downstage patients prior to complete metastasectomy has been considered. The largest retrospective study of this strategy contains data on only 22 patients and is difficult to interpret due to heterogeneity among subjects.

Role of Sunitinib, Everolimus Clarified in Non-clear Cell RCC

Metastatic non-clear cell RCC continues to be a challenge for researchers and clinicians alike. Andrew Armstrong, MD, presented the final results of the ASPEN trial, which randomized patients with metastatic papillary, chromophobe, or unclassified histology; any MSKCC risk group; and no prior systemic therapy to either everolimus or sunitinib in a 1:1 fashion;108 subjects across 17 sites and 3 countries were enrolled. The study found that sunitinib improved overall PFS, meeting the primary endpoint of the trial. Sunitinib also improved PFS in good/intermediate risk and papillary/unclassified patients, but everolimus improved PFS in poor risk and chromophobe patients.

In Papillary RCC, MET Alterations Found to Drive the Disease in a Subset of Patients

Daniel George, MD, presented a talk about papillary RCC. He discussed an abstract from Laurence Albiges and colleagues in which distinct MET alterations were found to define a MET driven subset of papillary RCC. This group analyzed 161 papillary RCC tumors and identified 3 distinct MET alterations, including a new recurrent splicing isoform of MET in 8 cases. MET-alterations were found largely in type 1 papillary RCC and were associated with lower grade, lower stage and longer overall survival.

He also discussed a phase 2 trial of everolimus and bevacizumab in advanced non-clear cell RCC, which showed efficacy in patients with RCC with papillary features in the frontline setting. [i] This study enrolled 34 patients and treated them will full dose everolimus and bevacizumab. Four of these patients had papillary features, while 14 were said to have "papillary features" (and would likely have been classified as papillary at most other institutions).

Those patients classified as papillary or with papillary features did extremely well, with a 39% overall response rate and a PFS of 12.9 months (95% CI: 10.9 – NR) and OS of 19.7 months (95% CI: 16.7 – NR) compared to those with no major papillary histology who achieved a 19% overall response rate with a median PFS of 1.9 months (95% CI: 1.6 – NR) and median OS of 10.3 months (95% CI: 7.9 – NR). Finally, George discussed Przemyslaw Twardowski's abstract of SWOG 1107, a phase 2 trial of tivantinib (ARQ197) versus tivantinib in combination with erlotinib in papillary RCC, which had disappointing results. [ii] The study was closed at interim analysis due to 0 responses in either arm. George theorized that perhaps the study drugs may have been directed at suboptimal targets or the drugs have failed to efficaciously inhibit the intended targets.

On the Horizon: New Targets and Pathways Elucidated

Among the most interesting summary presentations regarding renal cell carcinoma, was the talk given by James Larkin, MD of the Royal Marsden in London, entitled "New Pathways and Targets in Kidney Cancer." Dr Larkin discussed the possibility of augmenting the current anti-VEGF and mTOR therapy paradigms by boarding therapies to include those targeting more than one molecular target.

Dr Larkin discussed the results of the dual-PI3K/ TORC1/2 inhibitor apitolisib (GDC0980) vs everolimus, which showed worsen PFS with the study drug. Similarly, a study of the dual TORC 1/2 inhibitorAZDE2014 vs everolimus was stopped early due to worsening PFS in the study arm. Of course, results of the METEOR study of cabozantinib (dual anti-VEGF and anti-c-MET) are anxiously awaited.

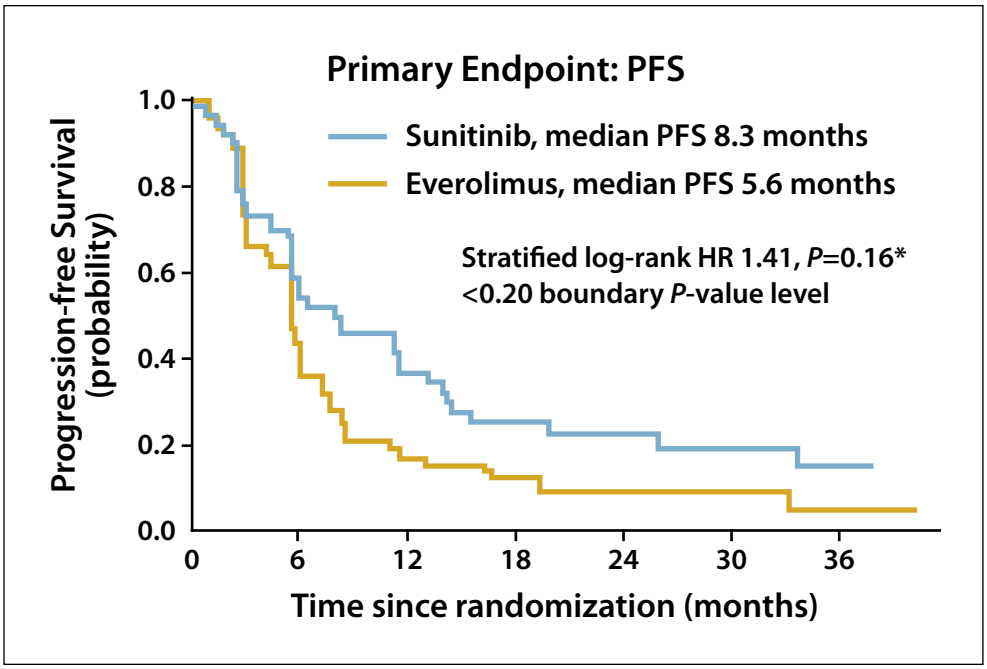

Figure 2. This trial randomized patients with metastatic non-clear cell to receive either everolimus or suntinib; 108 patients were randomized, and median PFS in the suntinib group was 8.3 months compared to 5.6 months in the everolimus group. This met the pre-defined criteria for statistical significance.

He presented discussed studies of combined targeted therapies, which have universally been disappointing. The practical use of combinations have been limited by toxicities that do allow for either therapy to be given at full dose, which may at least in part explain while these combinations have not been shown to increase efficacy.

Despite disappointing results to date, a few combination trials are ongoing. The DART study, a randomized phase 2 trial of single agent axitinib versus axitinib combined with the ALK1-directed trap dalantercept. Preliminary results of part 1 of the study showed a disease control (PR+SD) at 6 months of 57% (n = 16/29). The preliminary median PFS was 8.3 months for all dose levels combined. Expansion of the trial to 130 enrollees is ongoing. Likewise, a similar randomized phase 2 trial of single agent axitinib versus axitinib combined with the anti-endoglin antibody TRC105 is also ongoing. TRC105 combined with bevacizumab failed to prolong PFS compared to bevacizumab, in the California Clinical Consortium Trial presented at this meeting.[iii]

A Familiar Refrain: Resistance Remains a Tough Challenge

Dr Larkin echoed a frustration heard over and over regarding the clinical management of RCC—that there are no clinically relevant molecular predictors of disease response to therapy. Although most patients will get some efficacy from anti-VEGF targeted therapies, the biggest limitation to these treatments is that acquired resistance develops. Not characterized by activating kinase mutations. RCC is dominated by tumor suppressor genes—more difficult to target. The idea that "one size fits all" in the treatment of metastatic RCC, denies the inherit heterogeneity and complexity of the disease.

Table 2. Biomarkers associated with potential outcomes in study of nivolumab.

	PD-L1+ n = 18	PD-L1– n = 38
Median OS, mo (95% CI)		
Overall	NR	23.4 (13.1–33.3)
Previously treated	NR	22.3 (12.0–27.0)
Treatment-naïve	NR	33.3 (2.0–NR)
OS rate, % (95% CI)		
1-yr	71 (44–87)	71 (52–83)
2-yr	64 (37–82)	48 (30–64)

ASCO 2015 brought with it much data in the field of metastatic RCC. Despite recent excitement following the FDA approval of two targeted immunotherapies for lung and melanoma, a major theme ASCO 2015 in RCC is that we still have to wait from the largest trials of targeted immunotherapy to fully determine whether this new therapeutic option will be clinically beneficial in metastatic renal cell carcinoma as suggested by earlier studies. Until then, we continue to progress forward as novel therapies are tested, biology is further elucidated, and new data helps us better optimize therapies already in use.

Ten Posters That Made Us Pause and Think

The following is an abstracted selection of 10 RCC posters/abstracts from the 2015 Scientific Sessions of the American Society of Clinical Oncology that merit consideration as investigators addressed a broad spectrum of issues.

1. Predictors of renal dysfunction during everolimus treatment in patients with metastatic renal cell carcinoma. Authors: Ryuichi Mizuno, Ryohei Takahashi, Toshiaki Shinojima, et al. *J Clin Oncol*.33, 2015 (suppl; abstr e15584). A total of 31 patients with metastatic RCC treated with everolimus after after treatment failure with vascular endothelial growth factor receptor-tyrosine kinase inhibitor (VEGFR-TKI) were evaluated retrospectively. Analysis suggested that everolimus could be nephrotoxic in patients with mRCC who presented with renal dysfunction during prior VEGFR-TKI treatment.

2. Analysis of real world treatment compliance in a cohort of 2,395 patients with metastatic renal cell carcinoma (mRCC). Authors: Jay Margolis, Nicole Princic, Justin Doan, et al. *J Clin Oncol*. 33, 2015 (suppl; abstr 4546) In this retrospective cohort study, authors used administrative claims databases to select patients newly diagnosed with mRCC during 1/1/2006 to 3/31/ 2014. Compliance was measured using the medication possession ratio (MPR) during each and all lines of therapy. MPR was defined as total days of supply during the treatment period divided by the total treatment period until the start of the last treatment. The authors found that over half of treated mRCC patients in this study were noncompliant with therapy. Compliance was significantly better with IV administered temsirolimus relative to the reference oral therapy sunitinib.

3. Wild type *VHL* clear cell renal cell carcinomas: A distinct morphological and clinical entity with PD-L1 expression. Authors: Laurence Crouzet, Angelique Brunot, Julien Dagher, et al. *J Clin Oncol*. 33, 2015 (suppl; abstr 11053). In this study, the authors correlated the status of the *VHL* gene in 98 clear cell RCC cases with pathological criteria, expression of PDL1 and clinical outcome. 33.6% of the patients studied had 0 or 1 alteration (non inactivated *VHL*) *versus* 66.3% with 2 inactivating events (inactivated *VHL*). Non inactivated *VHL* was associated with a higher Fuhrman grade 4 ($P = 0.02$), metastases ($P = 0.04$), sarcomatoid component ($P = 0.01$) and dense lymphocyte infiltrate ($P = 0.013$). Furthermore, in this group, wild type *VHL* tumors (no alteration of the *VHL* gene, 11,2%), were particularly associated with PD-L1 expression ($P < 0,0001$), and had a worse outcome with a median specific survival of 33 months ($P = 0.016$).

4. Phase II study of Lutetium-177-labeled anti-Carbonic Anhydrase IX monoclonal antibody girentuximab in patients with advanced renal cell carcinoma. Authors: Marye Boers-Sonderen, Stijn Muselaers, Tim van Oostenbrugge, et al. *J Clin Oncol*. 33, 2015 (suppl; abstr e14014). In this single-center, non-randomized phase II trial, patients with progressive metastatic clear cell RCC received radioimmunotherapy with 2.4 GBq ^{177}Lu-labeled anti-CAIX antibody, girentuximab, if targeting of the antibody was observed after a diagnostic injection with ^{111}Indium labeled girentuximab. Patients were eligible for another treatment cycle if they had at least stable disease on evaluation after 3 months and did not have prolonged grade 4 hematological toxicity. Retreatment was at 75% of the previous activity dose with a maximum of 3 treatment cycles in total. 14 patients were enrolled in the study and received at least one infusion with ^{177} Lu-girentuximab. After the first treatment cycle stable disease was observed in 8 (57%) patients, partial response was seen in 1 (7%) patient, while progressive disease was seen in the other 5 (36%) patients. The treatment was generally well tolerated, but resulted in transient grade 3-4 leucocytopenia and/or thrombocytopenia in all, but one patient. Of the 9 patients with clinical benefit (PR,SD) after the first cycle, 3 patients were not eligible for retreatment due to prolonged hematological toxicity. After the second treatment cycle, continued SD was observed in 5 out of 6 patients. All 5 suffered from prolonged thrombocytopenia after cycle 2 and were therefore not eligible for the third treatment cycle.

5. Next generation sequencing of stool specimens from patients with metastatic renal cell carcinoma (mRCC) defines a bacterial profile associated with treatment-related diarrhea. Authors: Sumanta Kumar Pal, Sierra Mi Li, Yulan Lin, et al. *J Clin Oncol*. 33, 2015 (suppl; abstr e15580). In patients with metastatic RCC receiving vascular endothelial growth factor-tyrosine kinase inhibitors (VEGF-TKIs), diarrhea can be problematic. All grade diarrhea and grade 3-4 diarrhea occurs in roughly 50% and 10-15% of patients receiving VEGF-TKIs, respectively, but the etiology remains unknown. Eligible patients had metastatic RCC and were receiving an FDA approved VEGF-TKI. Stool was collected via a standardized protocol and total genomic DNA was isolated and PCR was used to amplify bacterial RNA. 20 patients were analyzed. Clustering based on incurred toxicity suggested that *Prevotella spp* and *Bacterioides spp* were negatively and positively associated with the risk of diarrhea, respectively ($P < 0.05$), suggesting that *Prevotella spp* may have a protective effect, while *Bacteroides spp* may be associated with a higher risk of VEGF-TKI-related diarrhea.

6. Randomized phase II study of two different doses of AVE0005 (VEGF Trap, aflibercept) in patients (pts) with metastatic renal cell carcinoma (RCC): An ECOG-ACRIN study [E4805]. Authors: Roberto Pili, Judith Manola, Michael Anthony Carducci, et al. *J Clin Oncol*. 33, 2015 (suppl; abstr 4549). AVE0005 (VEGF Trap), or aflibercept, is a recombinantly-produced fusion protein consisting of human VEGF receptor extracellular domains

fused to the F_c portion of human IgG_1 that has potent anti-VEGF activity. Patients with metastatic clear cell RCC and previous treatments including prior exposure to a VEGF TKI were stratified on prior immunotherapy (IL2/IFN) and MSKCC Risk Category. Patients received aflibercept (either 1 mg/kg or 4 mg/kg) day 1 of a 14-day cycle until progression. Patients randomized to 1 mg/kg could crossover to 4 mg/kg at progression. 94 pts were enrolled, 59 and 35 to 4 mg and 1 mg doses respectively. 16 eligible pts crossed over at progression to the 4 mg dose. The most common adverse events were hypertension, proteinuria, and fatigue. Only 4 pts reported Grade 4 or higher toxicity. With 36/59 (61%) pts PF at 8 wks, the 4-mg/kg dose met protocol specified efficacy criteria. These authors concluded that aflibercept at a dose of 4 mg/kg is active in previously treated ccRCC and may be worthy of further study.

7. HIF inhibition in metastatic renal cell carcinoma (mRCC): Final results of a phase Ib /IIa clinical trial evaluating the nanoparticle drug conjugate (NDC), CRLX101, in combination with bevacizumab (bev). Authors: Stephen Michael Keefe, Jean H. Hoffman-Censits, Ronac Mamtani, et al. *J Clin Oncol*. 33, 2015 (suppl; abstr 4543). *VHL* inactivation occurs in most clear cell RCCs and results in expression of the HIF hypoxia response program and ultimately leads to tumor angiogenesis. CRLX101, an NDC with a camptothecin payload, has been shown in preclinical models to durably inhibit both HIF1a and HIF2a. Synergy has been observed in the pre-clinical setting between this NDC and antiangiogenic agents including bevacizumab. Patients with refractory metastatic RCC were treated every 2 weeks with bev (10 mg/kg) and escalating doses of CRLX101 (12 mg/m^2, 15 mg/m^2) in a 3+3 phase I design. A phase IIa expansion cohort of 10 pts was treated at the RP2D. 22 response-evaluable patients were enrolled at two AMCs (12 clear cell, 5 papillary, 3 unclassified, 2 chromophobe). Patients had a median of 2 prior therapies, and all had at least 1 prior standard therapy. No dose-limiting toxicities were observed. CRLX101 at its RP2D (15 mg/m^2) combined safely with standard bevacizumab. The median PFS was 9.9 months. Overall response rate (ORR) was 23%, and 85% experienced either a partial response or stable disease as best response. A randomized phase II clinical trial in mRCC is enrolling patients.

8. A randomized, open-label, multi-center phase II study to compare bevacizumab plus sorafenib versus sorafenib for the third-line treatment of patients with metastatic renal cell carcinoma (NCT02330783). Authors: Jun Guo, Xi Nan Sheng, Zhihong Chi, et al. *J Clin Oncol*. 33, 2015 (suppl; abstr e15591). This study aimed to compare bevacizumab plus sorafenib versus sorafenib for the third-line treatment of patients with metastatic renal cancer. Eligible patients had metastatic renal cell carcinoma with clear cell, and had received 1st line treatment of sunitinib and 2nd line treatment of everolimus before enrollment. Patients were randomly allocated in a 1:1 ratio to receive bevacizumab plus sorafenib (bevacizumab 5mg/kg intravenously every two weeks plus sorafenib 400 mg twice daily) or sorafenib alone (sorafenib 400 mg, orally, twice daily). Thirty-three of a planned 106 evaluable patients have been enrolled. Thus far, the objective response rate was 11.1% in the combination group and 0% in the comparator arm, while the median progression-free survival was 6.5 months in the study and 3.5 months in the single-agent arm. The median overall survival has not been reached.

9. Randomized phase II study of sunitinib + CXCR4 inhibitor LY2510924 versus sunitinib alone in first-line treatment of patients with metastatic renal cell carcinoma. Authors: John D. Hainsworth, Joseph Ronald Mace, James Andrew Reeves, et al. *J Clin Oncol*. 33, 2015 (suppl; abstr 4547). CXCR4 and its only known ligand, SDF-1, are both overexpressed in tumor and vascular cells of clear cell RCC. LY2510924 is a selective peptide antagonist of CXCR4. Thus study compared the results of open-label treatment with LY2510924 + sunitinib vs sunitinib alone. Previously untreated metastatic clear cell RCC patients were randomized (2:1) to receive standard-dose sunitinib (50 mg qd for 4 weeks [wk], then 2 wk off) + LY2510924 (20 mg sc, qd) (Arm A) or sunitinib alone (Arm B). 72 and 36 pts were treated in Arms A and B, respectively. Median PFS was 8.1 and 12.3 months in Arms A and B, respectively (HR [95% CI]: 1.19 [0.73, 1.94]). The ORR was 30.6% in Arm A and 38.9% in Arm B. Most toxicities were similar in both arms, but there were more bleeding-related events (mostly grade 1 or 2) in Arm A than B (39% compared to 14%). More patients in Arm A discontinued treatment due to adverse events (18.1% compared to 8.3%). There were two deaths in Arm A were due to adverse events (pulmonary edema/respiratory arrest/cardiac arrest and intracranial tumor hemorrhage). The authors concluded that adding the CXCR4 inhibitor LY2510924 to sunitinib as first-line treatment for metastatic RCC was tolerated, but did not improve efficacy.

10. Incidence of osteonecrosis of the jaw (ONJ) in metastatic renal cell cancer patients (mRCC) treated with zoledronic acid (ZA). Authors: Fruzsina Gyergyay, Krisztian Nagyivanyi, Krisztina Biro, et al. *J Clin Oncol*. 33, 2015 (suppl; abstr e20649. Bisphosphonates are routinely used in the treatment of patients with metastatic RCC with bone metastases in order to reduce the risk of fracture and bone pain. Data from 210 consecutive patients treated with intravenous zoledronic acid for metastatic RCC, with bone metastases were reviewed. The incidence of osteonecrosis of the jaw has been retrospectively assessed over time since 2005. 149 patients received one or several types of targeted treatment (sunitinib, sorafenib, everolimus, temsirolimus, pazopanib), 61 pts. were treated only with immunoche-motherapy. Nine cases of osteonecrosis of the jaw were identified. Six of these patients received sunitinib, 2 were treated with sunitinib

and sorafenib and one patient received sunitinib, sorfenib, and everolimus. None of the 61 patients treated with immunochemotherapy alone identified to have osteonecrosis of the jaw. The authors concluded that the risk of osteonecrosis of the jaw in patients with metastatic RCC treated with targeted treatment and zoledronic acid exceeded 6%, suggesting that a potential synergic antiangiogenic effect of tyrosine kinase inhibitors and zoledronic acid may increase the risk of this dreaded adverse event.

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[iii] Dorff TB, Longmate J, Pal SK, et al. Bevacizumab (Bev) alone or in combination with TRC105 for metastatic renal cell cancer (mRCC): A California Cancer Consortium clinical trial. J Clin Oncol 33, 2015 (suppl; abstr 4542). KCJ

GUEST EDITOR'S MEMO *(continued from page 22)*

benchmark for future developments, there are a myriad of related issues not explored at this year's meeting. One of these is the use of surveillance guidelines and their adequacy in detecting recurrences of RCC. The report in this issue focuses on the extent to which these guidelines from two major scientific groups need to be reconsidered in view of their limitations in predicting the rate of recurrences of metastatic RCC. This is still clearly a work in progress, and we are likely to see new recommendations within the next year as these protocols are revisited and suggestions are made for their update to reliably detect the likelihood of recurrent RCC.

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Deconstructing RCC Surveillance Guidelines: How to Close the Gaps to Improve Detection of Recurrences

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It may not be adequate to follow the protocols of national groups and their guidelines for surveillance after surgery. Their protocols, although ambitious and recently upgraded, may fall short in a number of areas and current work to revise the guidelines will undoubtedly take note of underappreciated factors, including the location of the tumor and the duration of surveillance, influencing the rate of detection.

Recurrence rates after surgery for renal cell carcinoma (RCC) have been well studied, with several sets of surveillance guidelines issued during the last two years by the National Comprehensive Cancer Network (NCCN) and the American Urological Association (AUA). Despite these protocols, there has been scant information available on the ability of these surveillance guidelines to capture recurrences by determining the total number of recurrences that would be detected if patients were strictly observed for the length of time recommended for each location—abdomen, chest, bone, and other sites. If there is a lack of consensus in the literature on the ability of these guidelines to capture recurrences, then one would expect there is even wider variation in clinical practice because clinicians either over- or underutilize testing for certain patient groups.[1]

There is no definitive evidence to clarify which protocol is optimal. Until recently the two protocols by the aforementioned national groups varied significantly, therefore it is not surprising that there is confusion regarding follow-up strategies. To what extent does surveillance help with outcomes or harm quality of life? And how should surveillance be applied to various sites if the surveillance guidelines are rigorously followed? This area of management is rapidly evolving and in the next year, there will likely be additional evidence emerging regarding the merits of various protocols. Until these new reports emerge—and they are in progress now—it is important to reexamine the guidelines issued in 2013 and 2014. Only be reviewing the adequacy of these guidelines and identifying their limitations can investigators determine the optimal approach that balances patient benefit and health care costs.

Our review at the end of 2014[2] assessed the ability of the guidelines from NCCN and AUA to capture RCC recurrences and determine the duration of surveillance required to capture 90%, 95%, and 100% of recurrences. This review provides a brief summary of our evaluation. To reconcile the two sets of guidelines, the NCCN updated its recommendations to resemble the risk-adapted algorithm of the AUA.[3]

Evaluating the Guidelines: Stratification of Patients

The review of our renal tumor registry identified 3,803 patients treated with radical or partial nephrectomy for M0 sporadic RCC between 1970 and 2008. These patients were stratified as AUA low risk (pT1Nx-0) after partial (LR-partial) or radical nephrectomy (LR-radical) or as moderate /high risk (M/HR; pT2-4Nx-0/pTanyN1). To assess the ability of the guidelines, the study calculated the percentage of recurrences detected when following the 2013 and 2014 NCCN and AUA recommendations. Disease recurrence was defined as demonstrable metastasis on imaging studies or via biopsies at least 30 days after surgery; locations included abdomen, chest, bone, or other sites, (CNS and skin). The Medicare costs were also compared.

With a median followup of 9 years, 29.8% or 1,088 patients experienced a recurrence. The key findings on detection:

- 35.9% of recurrences were detected using 2013 NCCN recommendations.
- 68.2% were detected using 2014 NCCN recommendations.
- 66.9 were detected using AUA recommendations.
- All 3 protocols most frequently missed recurrences in the abdomen and among pT1Nx-0 patients.
- To capture 95% of recurrences, surveillance was re-

Keywords: Metastatic renal cell carcinoma, surveillance guidelines, duration of followup, bone, abdomen, chest

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Interview

How Are Surveillance Guidelines Likely to Change?

In an interview with the Kidney Cancer Journal, Bradley Leibovich, MD, discussed issues related to an evaluation of surveillance guidelines he and his colleagues published. Their evaluation examined protocols from two national medical groups.

Q. To what extent could your evaluation in the *Journal of Clinical Oncology* of 2014 NCCN (National Comprehensive Cancer Network) and AUA (American Urological Association) guidelines influence clinical decision making? Are there 3 or 4 "take home" messages that emerge from this study on duration of surveillance?

Dr Leibovich: It could have a potentially significant influence on decision-making. Guidelines as they are miss about one-third of recurrences. Extending how long patients are on surveillance may impact our ability to intervene in appropriate circumstances. This is theoretical as we do not have any data that earlier detection of recurrence will lead to better outcomes. We would, however, infer from the data on resection of oligometastatic RCC the conclusion that early detection and intervention would be helpful. This would be difficult to prove definitively. Of course we have to also remember and weigh the concerns that surveillance is expensive and is itself a potential negative for patients' quality of life due to anxiety with these visits.

Q. Do you think a site-specific approach or surveillance guideline will be a greater part of future guidelines (eg the findings on abdomen and location-specific recurrence patterns, particularly pT1Nx-0 patients)?

Dr Leibovich: I suspect that the guidelines will be modified to better risk stratify surveillance schemes. This should include different approaches to surveillance in the abdomen, thorax, and elsewhere and varied length all based on data.

Q. Will the findings on LR-radical vs LR-partial also play a greater role in development of new strategies, since this trend noted in the study is probably underappreciated by most clinicians?

Dr Leibovich: This likely represents our selection of cases for partial versus radical. Ultimately, the best model will use the most robust risk stratification to determine strategy for surveillance. It remains to be seen if surgical approach will be in the model but it certainly will need further study.

Q. Considering that there is no strong evidence that surveillance for RCC or detection of asymptomatic recurrences translates into a survival benefit, how will this fact shape the future debate over surveillance guidelines? To what extent should patient preference be considered in long-term surveillance?

Dr Leibovich: Although very difficult to prove, there are ample data that would lead clinicians to believe that there is potential benefit. I am not aware of any solid tumor that has definitive data supporting any follow up regimen. Nonetheless, we do it based on the assumption that it provides benefit. If we make that assumption, then the duration, intensity, and method of surveillance should be optimized.

Q. Will cost-effectiveness in this setting loom as a larger factor in determining appropriate recommendations for surveillance? Do you foresee further delineation of risk/benefit ratios?

Dr Leibovich: There is no question that this will be true. KCJ

quired for 15 years for low risk-partial, 21 years for low risk-radical, and 14 years for moderate/high risk patients.

- To detect one LR-partial patient the cost was $1,228.79 using 2013 NCCN criteria; $2,131.52 using 2014 NCCN recommendations; and $1,738.31 using AUA guidelines. To detect 95% of LR-partial recurrences, costs would total $9,856.82.

Comparing the 2013, 2014 NCCN vs AUA Guidelines

Both the 2014 NCCN and the AUA guidelines showed to be most limited for LR-radical patients, in which only 35.3% and 29.5% of recurrences were detected, respectively. Among the four recurrence locations, all of the guidelines were least likely to capture abdominal relapses, with only 19.2% detected by the 2013 NCCN guidelines, 59% detected by the 2014 NCCN guidelines, and 58.6% detected by the AUA guidelines. Overall, a greater percentage of recurrences were captured with the 2014 NCCN and AUA risk-adapted approaches.

Both the 2014 NCCN and the AUA guidelines showed to be most limited for LR-radical patients, in which only 35.3% and 29.5% of recurrences were detected, respectively. (2) Among the four recurrence locations, all of the guidelines were least likely to capture abdominal relapses, with only 19.2% detected by the 2013 NCCN guidelines, 59% detected by the 2014 NCCN guidelines, and 58.6% detected by the AUA guidelines. Overall, a greater percentage of recurrences were captured with the 2014 NCCN and AUA risk-adapted approaches.

Interestingly, LR-radical patients had significantly higher recurrence

rates compared with LR-partial patients at all locations except for the abdomen. Because of this finding, we as-

sessed differences in clinicopathologic features among the low-risk groups and found that LR-partial patients had less aggressive tumor characteristics. For example, LR-partial patients, compared with LR-radical patients, had more frequently papillary histology (25% *v* 14.9%, respectively; *P*,.001), a stage of pT1a (75.3% *v* 46.5%, respectively; *P* <.001), a smaller median tumor size (3 cm; IQR, 2.0 to 4.0 *v* 4.5 cm; IQR, 3.2 to 5.7, respectively; *P* < .001) and less sarcomatoid differentiation (1% *v*12%, respectively; *P*=.011).[2]

When assessing the total Medicare costs among guidelines, we found that a patient would incur the lowest cost, $1,228.79, if following the 2013 NCCN protocol. Among the 2014 NCCN and AUA guidelines, the highest surveillance costs, $3,700.87, would be incurred by patients with high-risk disease because of the longer recommended follow-up. Similarly, on account of longer follow-up, an LR-partial patient would incur a greater cost for surveillance than an

LR-radical patient . However, to capture 95% of all recurrences, all risk groups would incur greater costs than those appreciated using current guidelines. For example, per-patient surveillance costs would be $9,856.82 for the LR-partial group, $13,097.26 for the LR-radical group, and $11,189.99 for the M/HR group.

Future Directions: Implications for Revising the Surveillance Guidelines

The evaluation of the NCCN and AUA surveillance guidelines not only highlights gaps in detection likely to emerge over time, it raises a number of implications that will need to be considered as protocols are revisited and revised. For example, the lowest number of recurrences captured among all three guidelines occurred in patients who were pT1Nx-0 or those who developed an abdominal relapse. Overall, the risk-adapted approaches advocated by the 2014 NCCN and AUA guidelines allowed for a greater percentage of recurrences to be identified. Incorporating recurrence location into the risk stratification used by the AUA allowed us to understand which risk groups and relapse sites required longer follow-up than what has previously been recommended.

Indeed, site-specific considerations emerged as one of the most important messages from the evaluation. For example, previous reports suggest the extent to which a longer median time to recurrence could have a significant impact on the ability of guidelines to detect metastases. Levy et al[4] examined site-specific recurrence pat- terns among stage groups and found noticeable differences in time to recurrence. The median time to recurrence for lung metastases was 53 months (range, 30 to 67 months) inpT1patients, 31 months (range, 4 to 67 months) in pT2 patients, and 14 months (range, 5 to 59 months) in pT3 patients. Similar differences were observed among other recurrence sites such as bone, liver, and brain.8 (4)LR-radical vs LR partial: who merits more rigorous followup?

In a finding that may seem counterintuitive to some observers, the evaluation revealed intriguing differences in recurrence patterns based on whether radical or partial resection was performed. LR-radical patients were more likely to harbor adverse characteristics, such as increased tumor size, pT1b stage, and clear cell histology, which have all been associated with disease progression.[5,6]These results support that LR-radical patients seem to be at a higher risk of recurrence compared with LR-partial patients and may warrant more rigorous surveillance.

Still another dimension highlighted in the study concerns to what extent the length of followup may lead to undersurveillance among various groups. Even for high-risk patients, all three guidelines provide no specific recommendations beyond 5 years. Although the risk-adapted strategies of the 2014 NCCN and AUA protocols were more successful at capturing recurrences than the 2013 NCCN guidelines, these updated algorithms still showed considerable shortcomings. By limiting specific abdominal and chest recommendations to 3 years or less for low-risk disease, the2014 NCCN and AUA guidelines missed at least 60% of recurrences.

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Correlation of PD-L1 tumor expression and treatment outcomes in patients with renal cell carcinoma receiving sunitinib or pazopanib: results from COMPARZ, a randomized controlled trial. Choueiri TK, Figueroa DJ, Fay AP, et al. *Clin Cancer Res*. 2015 Mar 1;21(5):1071-7. doi: 10.1158/1078-0432.CCR-14-1993. Epub 2014 Dec 23.
Summary: The interaction of programmed death-1 ligand (PD-L1) with its receptor (PD-1) on T cells inactivates antitumor immune responses. PD-L1 expression has been associated with poor outcomes in renal cell carcinoma (RCC) but has not been investigated in advanced RCC patients receiving VEGF-targeted therapy. Formalin-fixed paraffin-embedded specimens were collected at baseline from patients in the COMPARZ trial. Tumor cell PD-L1 expression by IHC was evaluated using H-score (HS). Dual PD-L1/CD68 staining was used to differentiate PD-L1 tumor expression from tumor-associated macrophages. Intratumor CD8-positive T cells were quantified morphometrically. Associations between biomarkers and survival were investigated using the log-rank test. HS data were available from 453 of 1,110 patients. Sixty-four percent of patients had negative PD-L1 expression (HS = 0). Patients with HS > 55 (n = 59, 13%) had significantly shorter overall survival (OS) than those with HS ≤ 55 in both pazopanib and sunitinib arms (median 15.1 vs. 35.6 and 15.3 vs. 27.8 months, respectively, $P = 0.03$). In both arms, median OS was shortest in patients with HS > 55 and intratumor CD8-positive T-cell counts > 300 (9.6 and 11.9 months with pazopanib and sunitinib, respectively). Median OS in patients with HS ≤ 55 and CD8-positive T-cell counts ≤ 300 was 36.8 and 28.0 months with pazopanib and sunitinib, respectively. Progression-free survival results were similar to OS results.
Conclusion: Increased tumor cell PD-L1, or PD-L1 plus tumor CD8-positive T-cell counts, were associated with shorter survival in patients with metastatic RCC receiving VEGF-targeted agents. These findings may have implications for future design of randomized clinical trials in advanced RCC.

Nivolumab for Metastatic Renal Cell Carcinoma: Results of a Randomized Phase II Trial. Motzer RJ, Rini BI, McDermott DF, et al. *J Clin Oncol*. 2015 May 1;33(13): 1430-7. doi: 10.1200/JCO.2014.59.0703. Epub 2014 Dec 1.
Summary: This phase 2 trial assessed the antitumor activity, dose-response relationship, and safety of nivolumab in patients with metastatic renal cell carcinoma (mRCC). Patients with clear-cell mRCC previously treated with agents targeting the vascular endothelial growth factor pathway were randomly assigned (blinded ratio of 1:1:1) to nivolumab 0.3, 2, or 10 mg/kg intravenously once every 3 weeks. The primary objective was to evaluate the dose-response relationship as measured by progression-free survival (PFS); secondary end points included objective response rate (ORR), overall survival (OS), and safety. A total of 168 patients were randomly assigned to the nivolumab 0.3- (n = 60), 2- (n = 54), and 10-mg/kg (n = 54) cohorts. One hundred eighteen patients (70%) had received more than one prior systemic regimen. Median PFS was 2.7, 4.0, and 4.2 months, respectively ($P = .9$). Respective ORRs were 20%, 22%, and 20%. Median OS was 18.2 months (80% CI, 16.2 to 24.0 months), 25.5 months (80% CI, 19.8 to 28.8 months), and 24.7 months (80% CI, 15.3 to 26.0 months), respectively. The most common treatment-related adverse event (AE) was fatigue (24%, 22%, and 35%, respectively). Nineteen patients (11%) experienced grade 3 to 4 treatment-related AEs.
Conclusion: Nivolumab demonstrated antitumor activity with a manageable safety profile across the three doses studied in mRCC. No dose-response relationship was detected as measured by PFS. These efficacy and safety results in mRCC support study in the phase 3 setting. KCJ

Horizon Pharma Collaborating With Fox Chase Cancer Center to Study ACTIMMUNE(R) Interferon gamma-1b in Combination With PD-1/PD-L1 Inhibitors

Philadelphia—Horizon Pharma plc, a biopharmaceutical company, announced a collaboration with Fox Chase Cancer Center to study Actimmune (interferon gamma-1b) in combination with PD-1/PD-L1 inhibitors in various forms of cancer including advanced urothelial carcinoma and renal cell carcinoma.

Preclinical cell line research has indicated that interferon gamma enhances cellular PD-L1 expression on endothelial cells and on some tumor cells. By enhancing cellular PD-L1 expression on tumor cells, interferon gamma may promote or enhance the effect of the PD-1 or PD-L1 inhibitors.

"This collaboration with Fox Chase Cancer Center is an important step in determining if the addition of ACTIMMUNE to a treatment regimen including a PD-1 and PD-L1 inhibitor can enhance the effect of these agents and potentially improve patient outcomes," said Jeffrey Sherman, MD, FACP, executive vice president, research and development and chief medical officer, Horizon Pharma plc. "Through this research, our goal is to gain a better understanding of the potential for Actimmune along with PD-1 and PD-L1 inhibitors in different patient populations and disease areas."

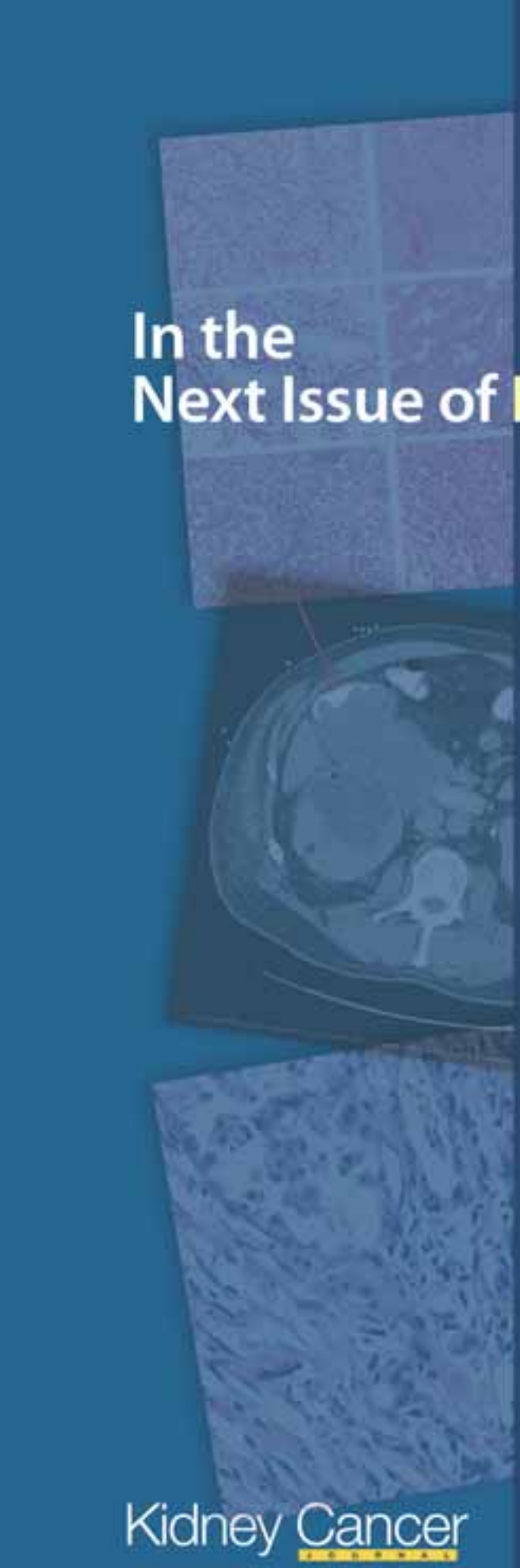
The first study being planned as part of the collaboration will be a dose-ranging study to determine a suitable dose for Actimmune with PD-1/PD-L1 inhibition. Once the ideal combination strategy is determined, the investigators intend to expand the study to include patients with metastatic bladder and renal cell carcinomas. Additional studies are expected to follow depending on initial results.

Timing of Maximum Tumor Shrinkage May Predict mRCC Patient Survival

NEW ORLEANS—The timing of maximum tumor shrinkage in patients with metastatic renal cell carcinoma (mRCC) may be useful as a biomarker for predicting overall survival, Japanese researchers reported at the 2015 American Urological Association annual meeting.

Takafumi Yagisawa, MD, and colleagues at Tokyo Women's Medical University, based this conclusion on a study of 199 mRCC patients receiving first-line systemic therapy with targeted agents. The study showed that the 81 patients who had maximum tumor shrinkage within 3 months—as measured by computed tomography (CT)—had significantly longer overall survival than the 48 patients who had maximum shrinkage after 3 months (22.8 vs. 14.3 months).

The agents used for first-line therapy included sunitinib (71 patients), sorafenib (47 patients), pazopanib (4 patients), and temsirolimus (7 patients). KCJ



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