The Cabozantinib Story: From Bench to Bedside

- Motility, invasion and metastasis
- Resistance to VEGFR TKIs
- Angiogenesis (HGF/MET)

HGF
GAS6
MET
AXL
HIFα
CABOZANTINIB
VEGF
TUMOR CELL
- Angiogenesis

Challenges in RCC Imaging

KCA Meeting Highlights

About the Cover
Mutation of the VHL gene is the predominant genetic lesion in clear cell RCC, which promotes stabilization of the HIF transcription factors and upregulation of hypoxia-associated genes, including VEGF, MET and AXL. Upregulation of VEGF promotes angiogenesis in RCC and underlies the efficacy of VEGF targeted agents in this disease. MET and AXL promote tumor invasiveness and metastasis, and are associated with the development of resistance to VEGFR inhibitors. Cabozantinib targets the MET and AXL pathways, along with the VEGF pathway, and therefore may provide enhanced disease control in this clinical setting.

KCJ GUEST EDITOR'S MEMO

What Is the Paradigm for Immunotherapy in RCC?

KCA Meeting Raises Key Questions to Reshape Our Approaches

David McDermott, MD

For more than two decades, the clinical experience with high dose (HD) IL-2 has provided proof of principle that immunotherapy can produce durable responses in a small percentage of patients with clear cell RCC (ccRCC) and obviate the need for subsequent therapy. However, its toxicity and limited efficacy has severely narrowed its application. Agents that induce a high proportion of durable tumor responses with acceptable toxicity remain a critical unmet need for mRCC patients. Ongoing clinical trials evaluating immune checkpoint blockade with CTLA-4 and PD-1/PD-L1 antibodies have demonstrated impressive clinical efficacy in many tumors and seem poised to shift the cancer treatment paradigm.

This edition of the *Kidney Cancer Journal* describes the results of the first, large randomized trial of PD-1 blockade in ccRCC patients who had failed prior therapy (Checkmate-025) (Motzer et al., *NEJM* 2015). In this pivotal trial, nivolumab produced clinically meaningful improvements in overall survival and quality of life, while displaying a favorable toxicity profile. Importantly, PD-1 pathway blockade led to a durable benefit without the toxicity associated with HD IL-2.

At the recent International Symposium of the Kidney Cancer Association, investigators debated ways in which we could build upon this new standard of care and optimize the therapeutic potential of PD-1 blockade based immunotherapy. Given the recent FDA approval of nivolumab (BMS) in RCC, several critical unanswered questions will likely pose an immediate challenge to patient management. For example, when can PD-1 blockade by safely discontinued? Does it need to be given for two years, indefinitely, or can some patient stop early and still achieve treatment-free survival?

Currently available data suggest that the answer may vary in different patients. Since most responses to PD-1 blockade occur early (< 6 months) and treatment can last for two years or beyond, it is likely that we are "over-treating" a subset of patients. But how do we identify those patients? This may require considering novel trial designs with novel endpoints, such as the sorafenib randomized discontinuation study that confirmed its clinical activity in RCC patients with stable disease.
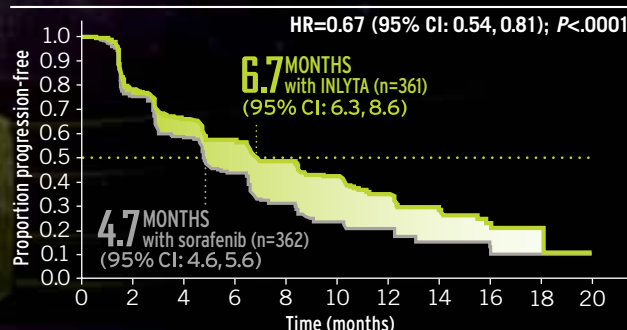
GIVE THEM A FIGHTING SECOND CHANCE

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

INLYTA—proven superior progression-free survival vs sorafenib in 2nd-line mRCC

Primary endpoint: progression-free survival (PFS)

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

6.7 MONTHS with INLYTA (n=361) (95% CI: 6.3, 8.6)

4.7 MONTHS with sorafenib (n=362) (95% CI: 4.6, 5.6)

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

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]

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

Important Safety Information

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

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

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

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

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

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

Please see Brief Summary on the following pages.

To learn more about INLYTA, visit ContinueTheFight.com

References: 1. Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. *Lancet.* 2011;378(9807):1931-1939. **2.** Data on file. Pfizer Inc, New York, NY. **3.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Kidney Cancer V.1.2016. © National Comprehensive Cancer Network, Inc 2015. All rights reserved. Accessed October 1, 2015. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

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

INLYTA® (AXITINIB) TABLETS FOR ORAL ADMINISTRATION
Initial U.S. Approval: 2012
Brief Summary of Prescribing Information

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

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

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

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

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

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

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

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

DOSAGE FORMS AND STRENGTHS
1 mg tablets of INLYTA: red, film-coated, oval tablets, debossed with "Pfizer" on one side and "1 XNB" on the other side.
5 mg tablets of INLYTA: red, film-coated, triangular tablets, debossed with "Pfizer" on one side and "5 XNB" on the other side.

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS
Hypertension and Hypertensive Crisis. In a controlled clinical study with INLYTA for the treatment of patients with RCC, hypertension was reported in 145/359 patients (40%) receiving INLYTA and 103/355 patients (29%) receiving sorafenib. Grade 3/4 hypertension was observed in 56/359 patients (16%) receiving INLYTA and 39/355 patients (11%) receiving sorafenib. Hypertensive crisis was reported in 2/359 patients (<1%) receiving INLYTA and none of the patients receiving sorafenib. The median onset time for hypertension (systolic blood pressure >150 mmHg or diastolic blood pressure >100 mmHg) was within the first month of the start of INLYTA treatment and blood pressure increases have been observed as early as 4 days after starting INLYTA. Hypertension was managed with standard antihypertensive therapy. Discontinuation of INLYTA treatment due to hypertension occurred in 1/359 patients (<1%) receiving INLYTA and none of the patients receiving sorafenib. Blood pressure should be well-controlled prior to initiating INLYTA. Patients should be monitored for hypertension and treated as needed with standard anti-hypertensive therapy. In the case of persistent hypertension despite use of anti-hypertensive medications, reduce the INLYTA dose. Discontinue INLYTA if hypertension is severe and persistent despite anti-hypertensive therapy and dose reduction of INLYTA, and discontinuation should be considered if there is evidence of hypertensive crisis. If INLYTA is interrupted, patients receiving antihypertensive medications should be monitored for hypotension.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Adverse Reaction[a]	INLYTA (N=359) All Grades[b] %	INLYTA (N=359) Grade 3/4 %	Sorafenib (N=355) All Grades[b] %	Sorafenib (N=355) 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

Kidney Cancer Journal Author Guidelines

Scope of Manuscripts
The *Kidney Cancer Journal* considers the following types of manuscripts for publication:
- Reviews that summarize and synthesize peer-reviewed literature to date on relevant topics in a scholarly fashion and format.
- Original contributions based on original, basic, clinical, translational, epidemiological, or prevention studies relating to kidney cancer that are well documented, novel, and significant.
- Letters to the Editor on timely and relevant subjects pertaining to the diagnosis and treatment of renal cell carcinoma.
- Clinical case studies.

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

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

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

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

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

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

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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, David F. McDermott, MD, for their timeliness, importance, relevance, and potential impact on clinical practice or translational research.

Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. Motzer RJ, Escudier B, McDermott D, et al. *N Engl J Med*. 2015 Nov 5; 373:1803-1813. doi: 10.1056/ NEJMoa1510665
Summary: This randomized, open-label, phase 3 study compared nivolumab with everolimus in patients with renal cell carcinoma (RCC) who had received previous treatment. A total of 821 patients with advanced clear-cell RCC for which they had received previous treatment with one or two regimens of antiangiogenic therapy were randomly assigned (in a 1:1 ratio) to receive 3 mg of nivolumab per kilogram of body weight intravenously every 2 weeks or a 10-mg everolimus tablet orally once daily. The primary end point was overall survival. Secondary end points included the objective response rate and safety. The median overall survival was 25.0 months with nivolumab and 19.6 months with everolimus. The hazard ratio for death with nivolumab versus everolimus was 0.73 (P=0.002), which met the prespecified criterion for superiority (P≤0.0148). The objective response rate was greater with nivolumab than with everolimus (25% vs. 5%; P<0.001). The median progression-free survival was 4.6 months with nivolumab and 4.4 months with everolimus (P=0.11). Grade 3 or 4 treatment-related adverse events occurred in 19% of the patients receiving nivolumab and in 37% of the patients receiving everolimus; the most common event with nivolumab was fatigue (in 2% of the patients), and the most common event with everolimus was anemia (in 8%).
Conclusion: Among patients with previously treated advanced RCC, overall survival was longer and fewer grade 3 or 4 adverse events occurred with nivolumab than with everolimus.

Everolimus Versus Sunitinib Prospective Evaluation in Metastatic Non-Clear Cell Renal Cell Carcinoma (ESPN): A Randomized Multicenter Phase 2 Trial. Tannir NM, Jonasch E, Albiges L, et al. *Eur Urol*. 2015 Nov 25. pii: S0302-2838(15)01083-0. doi: 10.1016/ j.eururo.2015.10.049.
Summary: Patients with metastatic, non-ccRCC, or ccRCC with >20% sarcomatoid features (ccSRCC) were randomized to receive sunitinib or everolimus with crossover at disease progression. Primary end point was progression-free survival (PFS) in first-line therapy; 108 patients were needed to show improvement in median PFS (mPFS) from 12 wk with sunitinib to 20 wk with everolimus. Interim analysis of 68 patients (papillary [27], chromophobe [12], unclassified [10], translocation [7], ccSRCC [12]) prompted early trial closure. The mPFS in first-line therapy was 6.1

mo with sunitinib and 4.1 mo with everolimus (P=0.6); median overall survival (mOS) was not reached with sunitinib and was 10.5 mo with everolimus, respectively (P=0.014). At final analysis, mOS was 16.2 and 14.9 mo with sunitinib and everolimus, respectively (P=0.18). There were four partial responses (PRs) in first-line therapy (sunitinib: 3 of 33 [9%]; everolimus, 1 of 35 [2.8%]) and four PRs in second-line therapy (sunitinib: 2 of 21 [9.5%]; everolimus, 2 of 23 [8.6%]), with mPFS of 1.8 mo and 2.8 mo, respectively. In patients without sarcomatoid features in their tumors (n=49), mOS was 31.6 mo with sunitinib and 10.5 mo with everolimus (P=0.075).
Conclusion: Everolimus was not superior to sunitinib. Both agents demonstrated modest efficacy, underscoring the need for better therapies in non-ccRCC. This randomized phase 2 trial provides the first head-to-head comparison of everolimus and sunitinib in patients with metastatic non-clear cell RCC.

Validation and genomic interrogation of the MET variant rs11762213 as a predictor of adverse outcomes in clear cell renal cell carcinoma. Hakimi AA, Ostrovnaya I, Jacobsen A, et al. *Cancer*. 2015 Oct 27. doi: 10.1002/ cncr.29765.
Summary: The exonic single-nucleotide variant rs11762213 located in the MET oncogene has recently been identified as a prognostic marker in clear cell RCC. This finding was validated with The Cancer Genome Atlas (TCGA) cohort, and the biologic implications were explored. The genotype status for rs11762213 was available for 272 patients. Paired tumor-normal data, genomic data, and clinical information were acquired from ccRCC TCGA data sets. Cancer-specific survival (CSS) was analyzed with the competing risk method, and Cox proportional hazards regression was used for the analysis of the time to recurrence (TTR). Multivariate competing risk models were fitted to adjust for the validated Mayo Clinic Stage, Size, Grade, and Necrosis (SSIGN) score. The variant allele of rs11762213 was detected in 10.3% of the cohort. After adjustments for the SSIGN score, the risk allele remained a significant predictor for adverse CSS P<.0001) and for TTR (P=.003). The mapping of rs11762213 to regulatory regions within the genome suggested that it might affect a DNA enhancer region. RNA and protein sequencing data for MET did not reveal differences in steady-state expression with stratification by risk allele.
Conclusion: The exonic MET variant rs11762213 is an independent predictor of adverse CSS and TTR in ccRCC and should be integrated into clinical practice for prognostic

Reshaping the Calculus of Kidney Cancer in 2016 and Beyond

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Celebrating its 25th anniversary and attracting 350 attendees to its venue in Miami, The Kidney Cancer Association offered a dynamic agenda at its 14th International Kidney Cancer Symposium, presenting new data, analyses, presentations and abstracts as part of the world's most comprehensive scientific program on renal cell carcinoma (RCC).

The program evaluated knowledge regarding clinical, molecular, genetic and biologic characteristics of RCC, assessed the effects of targeted therapy and immunotherapy, explored the use of novel agents and combinations of current approaches, reviewed options for minimally invasive management of localized and metastatic RCC, and presented information on future directions involving patients who develop progressive disease while on vascular endothelial growth factor (VEGF) therapy. All of the presentations, including slides and abstracts, and videos are available on the KCA website. For a complete review and virtual online program to the meeting, the following link is available: http://www.kidneycancer.org/ knowledge/learn/medical-education-cme/ (See the 2015 Miami meeting).

New findings on variant histology RCC and inherited VHL disease have emerged most recently and several presentations offered insights on chromophobe RCC, papillary RCC, collecting duct carcinoma, and RCC with sarcomatoid dedifferentiation. Related to these talks were new data on molecular and genetic characterizations of RCC and novel imaging techniques in RCC that could have translational impact, thereby obviating in some cases the need for renal mass biopsy.

Molecular and genetic characterization of RCC. Ari Hakimi, MD from Memorial Sloan Kettering Cancer Center summarized recently published data on molecular and genetic biomarkers in RCC, including subtyping of clear cell RCC using *BAP1* and *PBRM1* mutation status. In addition, data was presented on the discovery and validation sets studying the *MET* variant rs11762213 as a prognostic biomarker, and on the use of *BAP1*, *PBRM1,* and *KDM5C* mutational status as a predictive biomarker of response to targeted therapy in patients with RCC enrolled in the RECORD-3 trial (everolimus versus sunitinib). In addition, some insights into RCC using PanCancer genomics were discussed, including the fact that compared to other tumors, RCC has a modest mutation load, but a high immune infiltration. Ongoing research shows that using unsupervised clustering, clear cell RCC can be divided into 3 subtypes based on their immune infiltrating score: non-infiltrated, heterogeneously infiltrated, and T-cell enriched cluster. Potentially, these subtypes can be employed to better select patients for a more judicious use of checkpoint inhibitors.

Novel imaging techniques. The limitations of renal mass biopsy (RMB) and potential pitfalls associated with it have spurred interest in novel imaging techniques. There is the need for sedation or anesthesia with RMB, associated pain and discomfort, a low but albeit non-negligible nondiagnostic rate, a major complication rate of 1% among its drawbacks, and the inability of RMB to determine tumor grade accurately. A presentation by Michael Gorin, MD from Johns Hopkins University, focused on ongoing research using novel imaging techniques that can be potentially used to differentiate between various renal tumor histologies.

Emerging evidence suggests how nuclear/molecular imaging offers a promising and noninvasive means of determining renal tumor histology to achieve pretreatment risk stratification. Investigators at Johns Hopkins University used preoperative ^{99m}Technetium-sestamibi SPECT/CT to differentiate oncocytomas/hybrid oncocytic tumors from other renal tumors and found the technique had a sensitivity of 87.5% and a specificity of 95.2%.

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

FDA approves nivolumab to treat advanced form of kidney cancer

The FDA has approved nivolumab (Opdivo) to treat patients with advanced (metastatic) renal cell carcinoma, a form of kidney cancer, who have received prior antiangiogenic therapy.

"Opdivo provides an important therapy option for patients with renal cell carcinoma," said Richard Pazdur, MD, director of the Office of Hematology and Oncology Products in the FDA's Center for Drug Evaluation and Research. "It is one of few therapies that have demonstrated the ability to extend patients' survival in treating this disease." The National Cancer Institute estimates 61,560 new cases and 14,080 deaths from kidney and renal pelvis cancer in the United States this year.

"Additionally, Opdivo's extended indication, from melanoma and non-small cell lung cancer to renal cell cancer, demonstrates how immune therapies can benefit patients across a wide range of tumors," continued Dr Pazdur.

Opdivo works by targeting PD-1/PD-L1 (proteins found on the body's immune cells and some cancer cells). By blocking this pathway, Opdivo may help the body's immune system fight cancer cells. The safety and efficacy of Opdivo for this use were demonstrated in an open-label, randomized study of 821 patients with advanced renal cell carcinoma whose disease worsened during or after treatment with an anti-angiogenic agent. Patients were treated with Opdivo or everolimus (Afinitor). Those treated with Opdivo lived an average of 25 months after starting treatment compared to 19.6 months in those treated with everolimus. This effect was observed regardless of the PD-L1 expression level of patients' renal cell tumors. Additionally, 21.5% of those treated with Opdivo experienced a complete or partial shrinkage of their tumors, which lasted an average of 23 months, compared to 3.9 percent of those taking everolimus, lasting an average of 13.7 months.

ADAPT Phase 3 clinical trial of AGS-003 for metastatic RCC continues following second planned interim analysis

DURHAM, NC — Argos Therapeutics Inc., an immuno-oncology company focused on development and commercialization of fully individualized immunotherapies for the treatment of cancer based on the Arcelis® technology platform, announced its independent data monitoring committee (IDMC) has recommended continuation of the pivotal phase 3 ADAPT clinical trial of AGS-003 for metastatic renal cell carcinoma (mRCC) based on results of the committee's second planned interim data analysis.

"The ADAPT phase 3 trial to evaluate AGS-003 in front line mRCC, the largest global trial ever performed in newly diagnosed, unfavorable risk mRCC patients, continues to progress nicely," said Dr. Figlin, the Steven Spielberg Family chair in hematology oncology, professor of medicine and biomedical sciences at the Cedars-Sinai Samuel Oschin Comprehensive Cancer Institute and the principal investigator for the ADAPT trial. "We anticipate that we are approaching the mid-point for the expected number of events and look forward to the next interim review of the trial data in approximately six months."

AGS-003 is a fully individualized immunotherapy that captures mutated and variant antigens that are specific to each patient's tumor and is designed to induce an immune response targeting that patient's tumor antigens. 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 (intermediate and poor) risk mRCC patients. The randomized phase 3 ADAPT trial evaluating AGS-003 plus standard targeted therapy enrolled a total of 462 mRCC patients and has a primary endpoint of overall survival. AGS-003 is Argos' most advanced Arcelis-based product candidate.

Cerulean completes enrollment of randomized Phase 2 trial of CRLX101 in combination with Avastin® in relapsed RCC

CAMBRIDGE, MA—,Cerulean, a clinical stage company developing nanoparticle-drug conjugates (NDCs), has completed enrollment of a randomized Phase 2 trial of its lead NDC, CRLX101, in combination with Avastin®, in third- and fourth-line relapsed RCC. The trial has enrolled all 110 patients and the company expects to announce top-line data in the first half of 2016.

"This is an exciting time in the evolution of RCC treatments," said Martin H. Voss, MD, medical oncologist at Memorial Sloan Kettering Cancer Center and Principal Investigator for the trial. "Currently approved treatment options provide limited benefit to heavily pretreated patients, and the therapeutic approach in the third- and fourth-line setting is poorly defined. There remains a clear need for a different mechanistic approach, so I am pleased

METEOR Trial Milestones: Exciting Results Point Toward Potential Translational, Transformative Impact of Cabozantinib on RCCa

Robert A. Figlin, MD   Toni Choueiri, MD   Gisela Schwab,MD

*T*his Roundtable discussion focuses on phase 3 results from a pivotal clinical trial and how data emerging from it could reshape the treatment landscape in kidney cancer. The moderator is Robert A. Figlin, MD, Editor-in-Chief of the Kidney Cancer Journal. *The discussion includes Toni Choueiri, MD, Principal Investigator for METEOR, and Gisela Schwab, MD, Chief Medical Officer of Exelixis, a biopharmaceutical company focused on developing and commercializing small molecule therapies with the potential to improve the treatment of cancer. The company is the developer of cabozantinib.*

Dr Figlin: Describe the biologic properties of cabozantinib and how it differs from other already approved antiangiogenic drugs in RCCa.

Dr Schwab: Cabozantinib inhibits VEGF receptors and also targets MET and AXL. These are tyrosine kinases involved in angiogenesis, tumor cell proliferation and metastasis formation and are known to be associated with poor outcome in kidney cancer. MET and AXL are also thought to be involved in resistance development to VEGFR targeting therapy. So cabozantinib represents a novel mechanism of action, targeting the VEGFR but also additional relevant targets in the kidney.

Dr Figlin: In contrast to agents currently in use, such as sunitinib, cabozantinib also addresses other mechanisms and other pathways?

Dr Schwab: Yes, and particularly MET and AXL, that are relevant to kidney cancer.

Dr Figlin: Are there any other agents that address the MET pathway in this disease?

Dr Schwab: No, not in renal cancer.

Dr Figlin: What is the role of the MET pathway in RCC and how does it relate to angiogenic resistance and the use of cabozantinib?

Dr Schwab: In clear cell renal cancer the tumor suppressor Van Hippel Lindau (VHL) protein is inactivated resulting in dysregulation of hypoxia-inducible factors (HIFs). As a result VEGF, as well as MET and AXL are upregulated. Emerging preclinical and clinical data suggest that acquired resistance to VEGF pathway inhibition is associated with upregulation of such alternative proangiogenic and proinvasive signaling pathways, including the MET pathway. Cabozantinib inhibits VEGFRs, MET and AXL and may prevent or delay resistance development to VEGFR inhibitors. Based on the molecular pathobiology of RCC, there is a strong mechanistic rationale for the evaluation of cabozantinib in this disease.

Dr Figlin: The results of the phase 1 trial were quite promising. How did you use those results to design the pivotal phase 3 trial?

Dr Choueiri: As you mentioned, METEOR was based on the promising results from an earlier smaller RCC trial, as well as the results with cabozantinib in multiple malignancies. Very important and relevant to RCC is the fact that alternative pathways drive tumors that become resistant to VEGF inhibitors like sunitinib and others. A lot of data started coming out that the MET pathway and
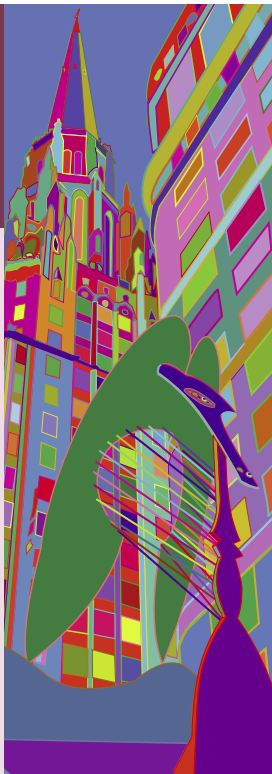
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more recently, the AXL pathway, can actually be targeted in the patient who develops resistance to VEGF inhibitors.

Dr Schwab: The phase 1 trial included 25 heavily pretreated RCC patients who had quite encouraging results with a response rate of 28% and a 12.9 months progression free survival. These results were certainly signaling activity and constituted one of the elements that supported the decision to go forward into phase 3.

Dr Figlin: Describe the pivotal trial design and the population of patients treated.

Dr Schwab: The METEOR trial was designed under the guidance and in collaboration with Toni Choueiri and members of the Study Steering Committee for the study. It was designed to evaluate the efficacy of cabozantinib as compared to everolimus in patients with advanced renal cell cancer who have received prior therapy with at least one VEGFR TKI. The patients could have received more than one TKI and also other agents such as bevacizumab or cytokines or PD-1 inhibitors. We did not limit the number of prior agents received. The primary endpoint was PFS and secondary endpoints included overall survival and objective response rate. For the primary endpoint assessment, PFS was determined among the first 375 patients enrolled. The secondary endpoint of overall survival was to be determined in the total study population and for that assessment to be adequately powered, we needed to a larger number of patients—650 patients.

Dr Figlin: Describe the results and assist the clinician in understanding how this can translate to their patients?

Dr Choueiri: The results showed that the primary endpoint of PFS was met. Cabozantinib resulted in a median PFS of almost double that of everolimus which is an active, standard second line therapy. The median PFS was 7.4 months with cabozantanib vs 3.8 months with everolimus. More interesting is the PFS among those patients who had only received sunitinib as their prior VEGFR TKI. In that case, when you go from sunitinib to cabozantinib, the PFS was 9.1 months and that compares favorably with everolimus and even in an indirect comparison with axitinib. The response rate was higher, four times more with cabozantinib—21%, vs 5% for everolimus.

Interestingly, it's important to mention an interim overall survival analysis, of cabozantinib. There was a promising trend favoring cabozantinib with only 49% of events. Hopefully, that will make us think more about being very optimistic with what is going to happen with overall survival when we have more events. If overall survival winds up being positive, then you will have a drug that improves all three efficacy endpoints, OS, PFS, and response rate.

Dr Schwab: As Toni mentioned, the data at the OS interim analysis were immature and the followup was very short at that time with only 6 months minimum followup. However, we are encouraged by the strong trend favoring cabozantinib in this analysis. Follow up is ongoing and the final analysis is expected in 2016.

Dr Figlin: Describe the impact of this treatment on RCC survival and the importance of this endpoint for physicians thinking about using this agent when compared to other choices. Secondly, please address the issue of dose limiting toxicities and how you would expect to manage the toxicity (ie, dose reductions).

Dr Schwab: At the planned interim analysis of OS data were immature; however, we have seen a strong trend favoring cabozantinib at this planned interim analysis. Follow up is ongoing and the final data are expected in 2016. Overall survival benefit has been elusive in the evaluation of VEGFR TKIs in RCC although various agents have shown PFS benefit. So OS is an important endpoint that could differentiate agents in this disease. Regarding the second question on tolerability: Clearly, the median exposure in the cabozantinib arms was much longer, 7.6 months vs 4.4 months for everolimus. The median average daily dose was 44 mg for cabozantinib and 9 mg for everolimus. Adverse events were managed with dose reductions and supportive care. The adverse event profile was generally consistent with what we've seen before with cabozantinib and with what has been reported for other VEGFR TKIs in this disease. In terms of numbers, there were 68% of patients who had Grade 3 or 4 adverse events on the cabozantinib arm and 58% on the everolimus arm. When we looked at the most frequent Grade 3 or 4 adverse events, on the cabozantinib arm it was hypertension, diarrhea, hand foot syndrome, and fatigue. On the everolimus arm it was anemia, fatigue, and hyperglycemia.

The frequency of serious adverse events was balanced between the treatment arms—40% and 43% for cabozantinib and everolimus, respectively. Adverse events were managed with dose modifications as described in the protocol. In the cabozantinib arm 60% of the patients had at least one dose reduction and that compares with 25% in the everolimus arm. Only 10% on both treatment arms experienced discontinuation. That suggests that dose modifications, including reduction, adequately addressed the management of adverse events, allowing patients to remain on study treatment for an extended period of time. If we're looking at how physicians are managing adverse events, it is through dose modification and dose reduction but also through supportive care. Frequent adverse events are diarrhea and hypertension, so

clearly, diarrhea medication is important to manage this adverse event, as are antihypertensive medications to manage hypertension.

Dr Figlin: Is it too early to mention intermittent dosing as a strategy as we've seen with some of the other agents for RCCa?

Dr Schwab: In a phase 1 study early on there was an intermittent dosing regimen for cabozantinib. But it has not been evaluated in later phase studies. Intermittent dosing is a possibility, but with the correct dose regimen and appropriate dose adjustment, we have manageable tolerability.

Dr Choueiri: I agree. This is not that different from most tyrosine inhibitors we use. The treatment discontinuation was around 10%. There is no secret here, that with many TKIs, you have to adjust the dose because of inter-patient variability in term of tolerance. Even now, after almost 10 years after the approval of sunitinib we are still coming up with alternative schedules.

Dr Figlin: How would a physician approach the use of cabozantinib when there are other agents in the second line setting that are available?

Dr Choueiri: This is a great time for patients. We have drugs that work. There are drugs in the VEGF- refractory setting now that do have efficacy. First of all, you have to take the efficacy into consideration. Which are the agents that are more efficacious—better PFS, better overall survival? Second, the tolerance of the drug, 3) the route of administration—IV vs oral. Does it matter for a patient coming a long way?

Dr Schwab: As Toni mentioned, it is great that physicians and patients will have more choices for advanced renal cell cancer that has been previously treated. Ultimately, sequencing of new agents, once available, and patient selection, will be important areas for research going forward.

Dr Figlin: What about patients with a poor prognosis? Do we know much about cabozantinib in that setting?

Dr Choueiri: One of the stratifications in the METEOR trial, and rightly so, besides the number of agents that target VEGFR, was the MSKCC risk groups. If you look at the MSKCC risk groups—between good, intermediate, and poor—you can clearly see that there is an advantage for cabozantinib over everolimus in all risk groups. So at this point, in my practice, I don't see an advantage of using everolimus in the average patient who is poor risk. Another thing about cabozantinib is the rate of progressive disease as the best response —only 14%. So I think that even in patients who have a very poor prognosis, and their disease is growing very fast and you need to hold the disease, cabozantinib can be attempted.

Dr Figlin: Are there additional plans to evaluate this approach in the front line setting or in any combinations? Is there a possibility that we may see a new clinical algorithm at ASCO 2016?

Dr Choueiri: At this time, we have a randomized phase 2 trial of cabozantinib vs. sunitinib in the front-line setting that finished accrual and may report in 2016.

Dr Schwab: Regarding other studies and with regard to what will be at ASCO, we don't know that yet, but will certainly provide updates when we get closer; there is an ongoing study evaluating cabozantinib in the first line setting and Toni is heading up that study. It is called CA-BOSUN. It's a randomized, phase 2 study done by the Alliance and CTEP. And it compares cabozantinib vs sunitinib in the first line setting for patients with RCC previously untreated and in in intermediate and poor risk categories. This is a study for which we hope to see results in the first half of 2016 and that we are certainly looking forward to. It is a study that potentially could inform further later stage evaluation of cabozantinib in the front line setting.

There is another ongoing study that is evaluating the combination of cabozantinib and nivolumab and the triple combination of the two agents plus ipilimumab in GU malignancies. It is currently ongoing at the NCI. I think it is an important trial because it will establish an optimal dose for the combination that can inform, again, further development of potential combination approaches in various indications but importantly, in RCC.

Dr Choueiri: We hope 2016 is going to clarify further strategies with cabozantinib and its place in the therapeutic armamentarium against kidney cancer. **KCJ**

METEOR: Results from the Randomized Phase 3 Trial of Cabozantinib

Thomas Powles[1], Bernard Escudier[2], Paul N. Mainwaring[3], Brian I. Rini[4], Frede Donskov[5], Hans J. Hammers[6], Thomas E. Hutson[7], Bruce Roth[8], Katriina Peltola[9], Jae Lyun Lee[10], Daniel Y. C. Heng[11], Manuela Schmidinger[12],

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INTRODUCTION

- Drugs targeting VEGF and its receptors, or the mammalian target of rapamycin (mTOR), are standard therapies in RCC
- Inactivation of the von Hippel-Lindau tumor suppressor protein in clear cell RCC results in upregulation of VEGF, MET, and AXL
- Increased MET and AXL expression has been associated with poor prognosis and resistance to VEGFR inhibitors in RCC
- Resistance to targeted therapy represents a major challenge to improving clinical outcomes of patients with RCC

CABOZANTINIB

- Cabozantinib is an oral small molecule inhibitor of tyrosine kinases including MET, VEGF receptors, and AXL
- A single arm trial of cabozantinib demonstrated clinical activity in heavily pretreated RCC patients
- The international, open-label phase 3 METEOR study evaluated the efficacy and safety of cabozantinib compared to everolimus in VEGFR tyrosine kinase inhibitor (TKI) pretreated RCC patients

STUDY DESIGN

- The objective of the Phase 3 METEOR study was to evaluate the efficacy and safety of cabozantinib versus everolimus in patients with advanced clear cell RCC following treatment with ≥ 1 VEGFR TKI
- Patients were randomized 1:1 to either receive cabozantinib 60 mg every day (qd) orally or everolimus 10 mg qd orally
- Stratification factors were as follows:
  - Number of prior VEGFR-targeting TKI therapies (1 vs 2 or more)
  - MSKCC prognostic criteria (0 vs 1 vs 2 or 3 risk factors)
- Crossover between treatment arms was not allowed

Figure 1. Study Design

STUDY END POINTS

- Primary end point: progression-free survival (PFS) per independent radiology committee (IRC)
- Secondary end points: overall survival (OS) and overall response rate (ORR)
- Additional end points: safety, quality of life, pharmacokinetics, pharmacodynamic analyses

ASSESSMENTS

- Radiographic tumor assessments including CT/MRI every 8 weeks (q8w), technetium bone scan q16w. After 12 months on study CT/MRI q12w, technetium bone scans q24w
- Routine safety evaluations were performed and adverse-event severity was assessed by the investigator with the use of the CTCAE criteria version 4.0

STATISTICAL DESIGN

- Primary endpoint: progression-free survival (PFS) among first 375 enrolled patients by IRC
  - 259 events to achieve 90% power
  - Hypothesized 50% increase in PFS (hazard ratio = 0.667)
- Secondary endpoints:
  - Overall survival (OS)
  - 408 events among 650 planned patients
  - Interim analysis at the time of primary PFS analysis
  - Objective response rate (ORR) by IRC

Figure 2. Study Populations and Design
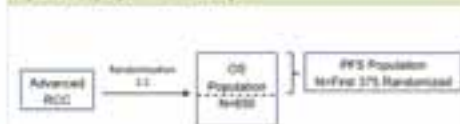
PATIENT DISPOSITION

- A total of 658 subjects were enrolled across 26 countries
- At the time of the primary PFS-endpoint analysis (cut-off: 22 May 2015), 40% of patients on the cabozantinib arm and 21% of patients on the everolimus arm remained active on treatment

BASELINE CHARACTERISTICS

- Baseline characteristics were balanced between the two treatment arms
- Majority of patients were of favorable to intermediate risk per MSKCC criteria

Table 1. Baseline Characteristics

Characteristic	Cabozantinib (N=330)	Everolimus (N=328)
Median age, years (range)	63 (32–86)	62 (31–84)
Male (%)	77	73
Enrollment Region, %		
Europe / North America	51 / 36	47 / 37
Asia Pacific & Latin America	14	16
ECOG Performance Status, %		
0	68	66
1	32	34
MSKCC risk group, %		
Favorable	45	46
Intermediate	42	41
Poor	12	13
Metastatic sites per IRC		
Lung	58	61
Liver	25	30
Bone	23	19

PRIOR THERAPIES

- The majority of patients received 1 prior VEGFR TKI
- The most common prior VEGFR TKI was sunitinib

Table 2. Prior Therapies

Characteristic	Cabozantinib (N=330)	Everolimus (N=328)
Number of VEGFR TKIs, %		
1	71	70
2 or more	29	30
VEGFR TKI, %		
Sunitinib	64	62
Pazopanib	44	41
Axitinib	16	17
Sorafenib	6	9
Other systemic therapy, %		
Cytokines	12	16
Nivolumab	5	4
Bevacizumab	2	3
Radiotherapy	33	33
Nephrectomy	85	85

PRIMARY ENDPOINT ANALYSIS OF PFS

- Treatment with cabozantinib resulted in highly statistically significant improvement in PFS, as assessed by an IRC, with a median PFS of 7.4 months for cabozantinib versus 3.8 months for patients treated with everolimus
- The minimum PFS follow up at the time of the primary PFS analysis was 11 months

Figure 3. PFS Among First 375 Enrolled Patients
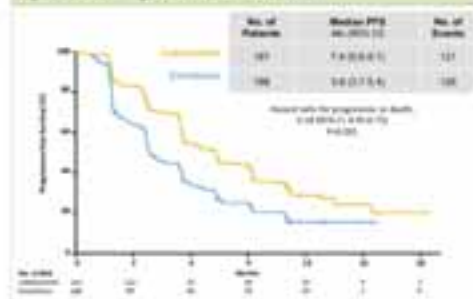
PROGRESSION-FREE SURVIVAL IN SUBGROUPS

- Progression-free survival benefit associated with cabozantinib was consistently observed in pre-specified subgroups defined according to the number of prior VEGFR TKIs and MSKCC prognostic risk group (Figure 4)
- In a post-hoc analysis of a subset of patients who received sunitinib as their only prior VEGFR inhibitor, which comprised 40% of the PFS population (n=151), the median PFS was 9.1 months for patients treated with cabozantinib compared to 3.7 months for patients treated with everolimus (Figure 5)

Versus Everolimus in Patients with Advanced Renal Cell Carcinoma (RCC)

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Figure 4. Progression-free Survival in Subgroups

Figure 5. PFS in Patients who had Received Sunitinib as the Only Prior VEGFR TKI
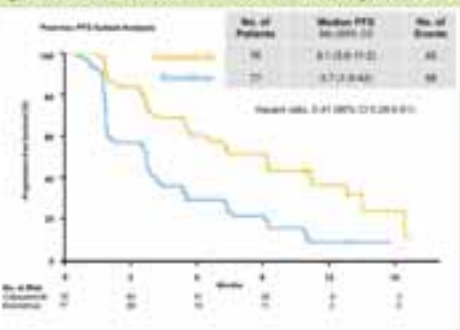
OBJECTIVE RESPONSE RATE

- Among the first 375 patients randomized, the ORR per IRC was 21% in patients on the cabozantinib arm and 5% in patients on the everolimus arm, and investigator assessed ORR was 23% versus 8% (p value <0.0011)
- The rate of primary refractory disease as indicated by PD as best overall response was lower on the cabozantinib arm (14%) compared to everolimus (27%)

Table 3. Objective response rate per IRC (PFS Population)

Objective response rate, %	Cabozantinib (N=187)	Everolimus (N=188)
95% CI	21	5
P value	16–28	2–9
		< 0.0001
Best overall response, %		
Complete response	0	0
Partial response	21	5
Stable disease	62	62
Progressive disease	14	27
Not evaluable or missing	3	6

BEST TARGET LESION CHANGE FROM BASELINE

- More patients in the cabozantinib arm achieved target lesion reduction as their best change from baseline, with 84% compared to 59% in the everolimus arm

Figure 6. Best Target Lesion Change from Baseline

INTERIM OVERALL SURVIVAL ANALYSIS

- Cabozantinib showed a strong trend for improved overall survival among all enrolled patients at the interim analysis, HR 0.67 (95% CI 0.51 to 0.89), p=0.005.
- With a minimum follow up of 6 months after the last patient enrolled, the interim boundary for significance was not yet reached and survival follow up is continuing until the final overall survival analysis is performed

Figure 7. Kaplan-Meier Estimates of Overall Survival

EXPOSURE AND DOSE REDUCTIONS

- Median duration of treatment with cabozantinib was 7.6 months and with everolimus 4.4 months.
- Two dose reduction levels were allowed to manage adverse events in both treatment arms. While there was a higher dose reduction rate in the cabozantinib arm compared to the everolimus arm (60% vs 20%), the rate for discontinuations for adverse events were similar (9% vs 10%)

SAFETY ANALYSIS

- The frequencies of any-grade and high-grade adverse events were similar in both treatment arms
- Frequent high grade adverse events in the cabozantinib arm were diarrhea, fatigue, PPE syndrome, and in the everolimus arm fatigue, anemia, hyperglycemia, pneumonitis

Table 4. All-causality Adverse Events

Preferred Term %	Cabozantinib (N=331)		Everolimus (N=322)	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Any adverse event	100	68	99	58
Diarrhea	74	11	27	2
Fatigue	56	9	46	7
Nausea	50	4	28	<1
Decreased appetite	46	2	34	<1
PPE syndrome	42	8	6	<1
Hypertension	37	15	7	1
Vomiting	32	2	14	<1
Weight decreased	31	2	12	0
Constipation	25	<1	19	<1
Anemia	17	5	39	16
Cough	18	<1	33	<1
Dyspnoea	18	3	29	4
Rash	15	<1	28	<1
Events of interest				
Hyperglycaemia	3	<1	19	3
Pneumonitis	0	0	10	2
GI Perforation	<1	<1	<1	<1
Fistula	<1	<1	0	0

CONCLUSIONS

- The METEOR phase 3 study met its primary endpoint, with cabozantinib nearly doubling median progression free survival compared to everolimus in patients with RCC who received prior VEGFR TKI therapy
- The objective response rate per independent radiology review was significantly improved with cabozantinib with a low rate of primary refractory disease
- Overall survival results at the interim analysis show a strong trend favoring cabozantinib
- Cabozantinib's safety profile is acceptable and tolerability is similar to other TKIs in this population
- Cabozantinib represents a potential new treatment option for second or later line therapy for RCC

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ACKNOWLEDGEMENTS

Challenges in RCC Imaging: Renal Insufficiency, Post-Operative Surveillance, and the Role of Radiomics

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Introduction

Renal cell carcinoma (RCC) is the third most common cancer of the genitourinary system and in 2015 will account for an estimated 61,560 new cases and 14,080 deaths in the United States.[1] Over the past several decades, the incidence of RCC has risen steadily by approximately 2-4% annually.[2] Imaging plays an integral role in the evaluation and management of a patient with a renal mass, from the preoperative workup to the postoperative surveillance. Unfortunately, in clinical practice the urologist is often faced with imaging dilemmas that lack definitive answers. Herein we explore the current data behind contemporary imaging topics, including imaging a patient with renal insufficiency, establishing a surveillance protocol after RCC therapy, minimizing radiation therapy during surveillance, and emerging imaging trends.

Imaging in the Setting of Renal Insufficiency

Contrast-enhanced studies are a crucial part of the evaluation of a renal mass. Contrast administration, however, is associated with various patient risks. One of the primary risks associated with iodinated contrast is contrast-induced nephropathy (CIN) (**Table**). CIN is the acute deterioration of renal function after the administration of IV iodinated contrast. There is no consensus definition of CIN though the Acute Kidney Injury Network (AKIN) definition includes one of the following criteria: absolute increase in serum creatinine of 0.3 mg/dL from baseline, a 50% increase in serum creatinine from baseline, or urine

output less than 0.5mL/kg/hour for at least six hours.[3]

It is widely agreed upon that past a certain degree of baseline renal insufficiency, iodinated contrast should not be administered. Unfortunately, there is poor evidence for defining this exact threshold. One survey of 420 radiologists revealed the three most common serum creatinine thresholds for avoiding iodinated contrast were 1.5, 1.7, and 2.0 mg/dL used by 35%, 27%, and 31% of radiologists, respectively.[4] The American College of Radiology Committee on Drugs and Contrast Media, however, notes that eGFR provides the best level of evidence for risk stratification of CIN and suggests that iodinated contrast can be safely administered in patients with eGFR â•30 mL/min/1.73m.[2,3]

Prevention of CIN is important to the urologist, especially given the anticipated nephron loss associated with many RCC treatments. Several preventative measures may be employed to help mitigate the risk of CIN. Intravenous hydration is the principle intervention shown to reduce the incidence of CIN and should be part of any mitigation protocol for at-risk patients receiving iodinated contrast.[5] Further, some data shows hydration with IV 0.9% saline is superior to 0.45% saline.[5] Another important principle is avoiding the use of high osmolality contrast media in patients with renal dysfunction, as level I evidence demonstrates its greater nephrotoxicity compared to low osmolality contrast media[6] (**Table**). Two other methods used to reduce the incidence of CIN, sodium bicarbonate and N-acetylcysteine, have had conflicting meta-analysis findings and consequently have significant variability in their clinical use. Given the clinical equipoise of these interventions, a prospective, randomized trial (The Prevention of Serious Adverse Events following Angiography (PRESERVE)) involving enrollment of 8680 patients is currently underway to provide definitive conclusions on the efficacy of sodium bicarbonate and N-acetylcysteine. Other interventions (e.g. endothe-

Table. Commmonly Used Iodinated Contrast Agents

Name	Compound	Iodine Content (mgl/mL)	Osmolality (mOsm/kg H2O)	
Hexabrix (Covidien)	Ionic	320	600	Low
Conray 43 (Covidien)	Ionic	202	1000	High
Hypaque 50 (Nycomed)	Ionic	300	1550	High
Visipaque 320 (GE Healthcare)	Nonionic	320	290	Low
Omnipaque 140 (GE Healthcare)	Nonionic	140	322	Low
Ultavist 300 (Bayer)	Nonionic	300	607	Low

lin-1, theophylline) are theoretically renoprotective yet have no data supporting their clinical use.

In patients at high-risk of developing CIN, efforts should be made to utilize alternative imaging including non-contrast CT, ultrasound, or MRI with gadolinium-based contrast agents (GBCAs) when possible. GBCAs, however, carry their own risk in patients with renal insufficiency, as they may develop nephrogenic systemic fibrosis (NSF). In the past, renal insufficiency was an absolute contraindication to receiving GBCAs. However, as the data associated with NSF was more carefully analyzed, it became clear that many patients with renal insufficiency could receive GBCAs with minimal risk. For instance, NSF in patients with eGFR > 30 ml/min/1.73 m2 is exceptionally rare and GBCAs can be safely administered.[3] The only caveat is that patients with eGFR of 30-40 should be treated similarly to those with eGFR <30, as eGFR may fluctuate on a day-to-day basis.

Patients with eGFR <30, and especially those with eGFR <15, are most at risk for NSF and so GBCA administration is not recommended in most cases. However, one literature review analyzed risk factor data based on 290 NSF cases and determined several key risk factors increased the incidence of NSF by approximately ten-fold each.[7] The most important were high dosage (>0.1 mmol/Kg) of GBCA, a delay in dialysis post-GBCA administration (for patients already on dialysis), and GBCA use during acute kidney injury. If these risk factors can all be avoided, the risk of NSF can be reduced by a thousand-fold. Another reported risk factor is the specific agent used, as three particular GBCAs (gadopentetate dimeglumine (Magnevist), gadodiamide (Omniscan), and gadoversetamide (Optimark)) are responsible for the majority of NSF cases and are contraindicated in at-risk patients.[8]

In summary, caution should be exercised when administering GBCA in patients with GFR <30. For those in whom GBCA-enhanced MRI is deemed necessary, only low-dose GBCA should be administered, hemodialysis should be initiated immediately following the procedure for patients on renal replacement therapy, injection of high-risk GBCAs should be avoided, and the study should not be performed in the setting of acute kidney injury. Moreover, alternative contrast-free methods, such as arterial spin labeling (ASL) per- fusion MRI or diffusion MRI, can be employed to provide useful diagnostic information.

Post-surgical Surveillance Imaging

Although surgical excision of organ-confined kidney cancer is often curative, local and distant recurrence rates vary by stage and histology.[9] Thus, the goals of surveillance imaging include detection of both metastasis and local recurrence at an early time point. Follow-up after RCC resection is individualized and based on the patient, risk factors for recurrence, which in turn can be predicted by several different models.

Both the 2015 NCCN and AUA guidelines on follow-up after treatment (PN or RN) of RCC use only TNM stage to stratify patients into risk groups[10,11] with subsequent follow-up regimens tailored to the specific groups. An as example, in both the NCCN and AUA guidelines, follow-up of a low risk pT1N0M0 patient entails baseline abdominal imaging (CT, MRI or US) within 3-12 months of surgery. Thereafter, patients treated with PN may optionally receive yearly abdominal imaging (CT, MRI, or US) for three years based on the presence of additional risk factors, while RN-treated patients need only undergo further abdominal imaging at the urologist, discretion. Finally, annual chest imaging is recommended for three years in all low risk patients. Another important consideration is surveillance following ablative therapies (i.e. cryoablation, radiofrequency ablation, and microwave ablation). Given that local recurrence is higher with ablative therapies, patients need to be followed more closely.[12] Current NCCN guidelines suggest baseline abdominal CT or MRI followed by five years of abdominal (CT, MRI, or US) and chest (CT or CXR) imaging. Finally, although non-ccRCC has very different outcomes compared to ccRCC, surveillance protocols are independent of histology. Thus, the onus is on the clinician to institute less rigorous surveillance for more indolent tumors (e.g. chromophobe) or more vigilant follow-up for more aggressive tumors (e.g. papillary type 2).

While stage-based surveillance protocols are straightforward and benefit from relative ease of use, alternative surveillance scoring systems and nomograms have been developed that¬†utilize both clinical and pathological variables to stratify patients and predict the likelihood of tumor recurrence. For instance, the UCLA Integrated Staging System (UISS) places postoperative RCC patients into low, intermediate, and high-risk strata based on Fuhrman nuclear grade, ECOG PS, and T stage[13], while the Leibovich model uses tumor stage, regional lymph node status, tumor size, Fuhrman nuclear grade, and histologic tumor necrosis to predict metastatic recurrence after radical nephrectomy for ccRCC. However, none of the pro-

posed models in the literature is free from error in delineating high-risk from low-risk patients, as a review of all postoperative models assessing recurrence showed C-indices range from 74%-82.2%.[14] Despite the accuracy limitations of the various models, the 2014 EAU Guidelines on Renal Cell Carcinoma recommend that the clinician choose a risk-stratifying model for use in practice.[15]

Importantly,¬†however, no level I evidence exists on which to base surveillance protocols, as the literature is based only on observational and case study data. The AUA surveillance guideline notes inconsistent outcomes when attempting to incorporate grade or other prognostic factors, and therefore settled on using TMN stage as the sole risk stratification metric. Data, however, indicate that urologists often do not follow a risk-adapted approach to surveillance imaging as suggested by the guidelines.[16] An analysis of the Surveillance, Epidemiology and End Results (SEER)-Medicare database revealed that surveillance imaging is over-utilized in low risk patients (e.g. pT1) while under-utilized in high risk patients (e.g. pT3) following nephrectomy.[17] Moreover, a recent study by Stewart et al. suggests that the current AUA and NCCN guideline recommendations may be inadequate for detecting recurrences.[18] They analyzed 3,651 patients who underwent RN or PN for M0 RCC and determined the number of recurrences when following the 2014 NCCN and AUA guidelines for surveillance. At a median of 9 years, almost one third of patients will have developed a recurrence that was missed by the 2014 NCCN and AUA guidelines. These findings suggest that current surveillance guidelines should become more intensive. On the other hand, as Smith et al. pointed out in an editorial response, extending the surveillance guidelines based on this study might be premature.[19] The most important reason is that the overall survival benefit of increased surveillance after RCC therapy is unproven. Further, there are multiple drawbacks to increased surveillance, including increased cost, effect on quality of life, and the risks of radiation exposure. In particular, the Medicare costs of surveillance based on current guidelines range from from $898 to $3,701, yet would rise to over $10,000 or more if surveillance were lengthened to capture 95% of RCC recurrences.

One response to the acknowledged inadequacies of the current guidelines is a novel, risk-based surveillance model that balances the risk of recurrence with the risk of non-RCC death. The Mayo Clinic developed a model that incorporates Charlson comorbidity index (CCI), pathologic tumor stage, and relapse location-specific data to predict the optimal duration of surveillance.[20] For instance, in an 80 year-old patient with pT1Nx-0 RCC and CCI of 1 or less, the risk of abdominal recurrence only exceeds the risk of non-RCC for a six-month period postoperatively. Therefore, in this example, surveillance is not warranted for more than six months and excessive costs, radiation exposure, etc. are avoided. Conversely, in a 50 year-old patient with pT1Nx-0 disease and a CCI of 1 or less, the risk of abdominal recurrence exceeded the risk

of non-RCC for a 20-year period, indicating surveillance for longer than current guideline recommendations is warranted.

Another promising alternative to more intensive or lengthier surveillance methods is tailoring recurrence risk and surveillance to the individual patient, RCC tumor biology rather than TNM stage as used in AUA/NCCN guidelines. For example, one large retrospective analysis of 472 total patients with sporadic ccRCC showed median overall survival was significantly shorter in the BAP1-mutant group compared to the PBRM1-mutant group (4.6 vs. 10.6 years, P=0.044).[21] Further, a 16-gene signature (Oncotype DX) recurrence score was recently validated in 626 patients as a predictor of recurrence after nephrectomy in stage I-III ccRCC. Knowing that different ccRCC gene mutations have different survival profiles may lead to better recurrence risk stratification and future surveillance guidelines.

Another challenge related to post-RCC treatment surveillance is balancing the need for intensive surveillance with the attendant risks of radiation exposure including the development of radiation-induced malignancies. The lifetime risk of a secondary malignancy related to surveillance after RCC treatment is largely unexamined. However, the risk is likely non-trivial. For instance, an estimation of lifetime cancer risk was calculated by Tarin et al. based on a five-year NCCN surveillance protocol for stage I nonseminomatous germ cell tumors of the testis.[22] By their calculations, a 40-year-old patient has a lifetime cancer risk of 1 in 61 (1.6%) after undergoing sixteen CTs of the chest/abdomen/pelvis in a five-year period. By comparison, an intermediate risk RCC patient following the UISS surveillance protocol would undergo thirteen chest CTs and five abdominal CTs over a ten-year period. Moreover, one study retrospectively analyzed the post-surgical surveillance of 315 patients with a pT1a RCC and found the relative risks of radiation-related solid cancers and leukemia were 1.05 and 1.12, respectively.[23] Again, these are small but non-negligible risks, especially in younger patients with RCC. Additionally, the absence of uniform surveillance regimens further complicates the issue of defining radiation risk. One review revealed that twelve total surveillance regimens exist in the literature with widely varying levels of radiation. For example, in a pT1b RCC lesion, if surveillance protocols were strictly followed a sample patient would receive anywhere from 0.5-450 mSv of cumulative radiation depending on the specific protocol.[24] Overall, it is clear that surveillance protocols pose a small but non-trivial risk of secondary malignancy, though the exact risk is poorly defined and protocol-dependent. Given the available data, modalities that lack ionizing radiation (e.g. MRI and US) should be considered in surveillance, especially in those patients with a long life expectancy and those with a low-risk of recurrence (e.g. T1a tumors).

In short, current guidelines and the majority of urologists favor the TNM staging system for its simplicity, though more sophisticated tools (e.g. nomograms, gene

signatures, etc.) may ultimately play a larger role in the future given recent data on missed recurrences. The most important questions requiring further study include whether surveillance impacts overall survival and the optimal timing and duration of surveillance to best detect metastases. Finally, it should be noted that the above strategies are applicable to surgical extirpation of RCC. Less data is available for surveillance after ablative therapies, though theoretically surveillance should be more rigorous given the higher rate of local recurrence in these treatments.

Contemporary Trends and Future Investigation

An important point to note is that renal masses represent a heterogeneous group of tumors that may be subdivided into various histological entities with different survival and oncologic outcomes. For instance, up to 30% of surgically resected kidney tumors less than 4cm in size will have a benign pathology (e.g. oncocytoma, angiomyolipoma).[25-27] Further, a significant portion of small renal masses (SRMs) are of the chromophobe or papillary type I RCC subtype, both of which portend a significantly better disease specific survival compared to clear cell RCC (ccRCC) histology.[28,29] There is thus a definite advantage to preoperatively identifying the histology of a SRM, as both the benign and less aggressive tumors (i.e. low-grade clear cell, papillary type I and chromophobe) could potentially be managed with active surveillance whereas more aggressive tumors should be surgically removed. However, no imaging modality has yet proven capable of reliably differentiating benign from malignant tumors or distin- guishing between the histologic subtypes of the malignant tumors.[30] Of note, biopsy-based risk stratification is emerging as a potentially viable option to determine active surveillance versus surgical excision, but biopsy remains an inherently invasive procedure with a risk of morbidity.[31] Ideally, a patient could preoperatively undergo a non-invasive imaging study to ascertain the histology of the renal mass. Molecular imaging modalities may be able to help bridge the gap between structural imaging (CT/MRI) and histologic diagnosis (biopsy).

Molecular Imaging

The paradigm may be changing with the introduction of iodine-124 (124I), cG250 PET/CT, a novel molecular imaging biomarker specific for ccRCC. This modality takes advantage of the fact that clear cell RCC overexpresses the enzyme carbonic anhydrase IX (CAIX), while non-clear cell RCC and normal tissues do not. Furthermore, the chimeric monoclonal antibody cG250 (girentuximab) specifically targets CAIX, allowing the radiotracer 124I-girentuximab to localize in ccRCC on PET/CT.

Two clinical trials thus far have investigated the potential of 124I-girentuximab PET/CT to preoperatively detect ccRCC. The first was a phase I pilot study, in which 26 patients with renal masses scheduled to undergo surgical resection were given 124I-girentuximab.[32] The preliminary results were quite favorable: 15/16 ccRCC and 9/9 non-ccRCC masses were correctly identified on preoperative PET/CT, with 94% and 100% sensitivity and specificity, respectively. A phase III open-label trial (REnal Masses: Pivotal Study to DETECT Clear Cell Renal Cell Carcinoma With Pre-Surgical PET/CT [REDECT]) was subsequently conducted at fourteen centers.[33] In this trial, 195 patients with renal masses were administered (124)I-girentuximab and preoperative PET/CT was then performed. The imaging findings were then compared to the histopathology. The results echoed those of the phase I trial: average sensitivity, specificity, positive predictive value, and negative predictive value of (124)I-cG250 PET for preoperative identification of ccRCC was 86.2% (95% CI, 75.3% to 97.1%), 85.9% (95% CI, 69.4% to 99.9%), 94.4%, and 69.4% respectively. The implications of these trials are far-reaching. As described above, the indeterminate SRM poses a clinical dilemma with multiple management options, including active surveillance, biopsy, ablation, and surgical excision.[34] Preoperative knowledge of the histology could reduce a number of unnecessary surgeries for benign renal masses and indolent RCCs and could ultimately supplant the renal mass biopsy.
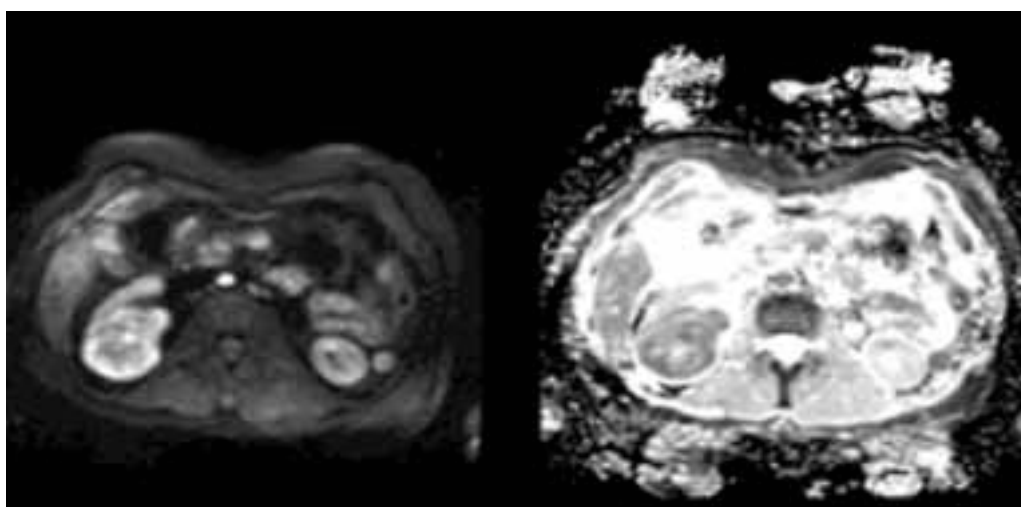
While the results of the phase III trial is certainly optimistic, as Khandani et al. pointed out in their review of the data, important questions must be answered before this test plays a role in the routine management of the indeterminate SRM.[37] First, the study did not examine just SRMs but also included renal masses up to 22cm. Moreover, analysis of the T1a subgroup showed a sensitivity of just 70.8% for masses less than or equal to 2cm, while failing to supply PPV, NPV, or specificity values for this subgroup. The main utility of this imaging modality is in the workup of the SRM and so more essential data related to SRMs is needed before this molecular imaging test reaches routine clinical practice. In addition, a technical concern raised by Khandani et al. is that the PET/CT scanners currently utilized by hospitals are inadequately equipped for adjustments related to optimal imaging of SRMs; that is, prompt Œ≥ correction and longer acquisition times may be needed for proper image quality but simply are not available on the typical hospital‚Äôs PET/CT machine.[35] Finally, in the event that 124I-girentuximab PET/CT does not detect ccRCC, the histology and malignant potential of the mass remains unknown. This may be a common scenario given that non-ccRCC accounts for approximately 25% of kidney tumors. In short, this technology is promising and may significantly alter the clinical practice of a SRM but both technical considerations and the need for additional data may limit its immediate impact.

Perfusion MRI and Diffusion MRI

Like (124I), cG250 PET/CT, perfusion MRI and diffusion MRI are contemporary imaging technologies that may provide information about tumor histology as well as physiology. Perfusion MRI examines the microcirculation at the capillary level. There are three perfusion MRI methods: Dynamic Contrast Enhanced (DCE), Dynamic Sus-
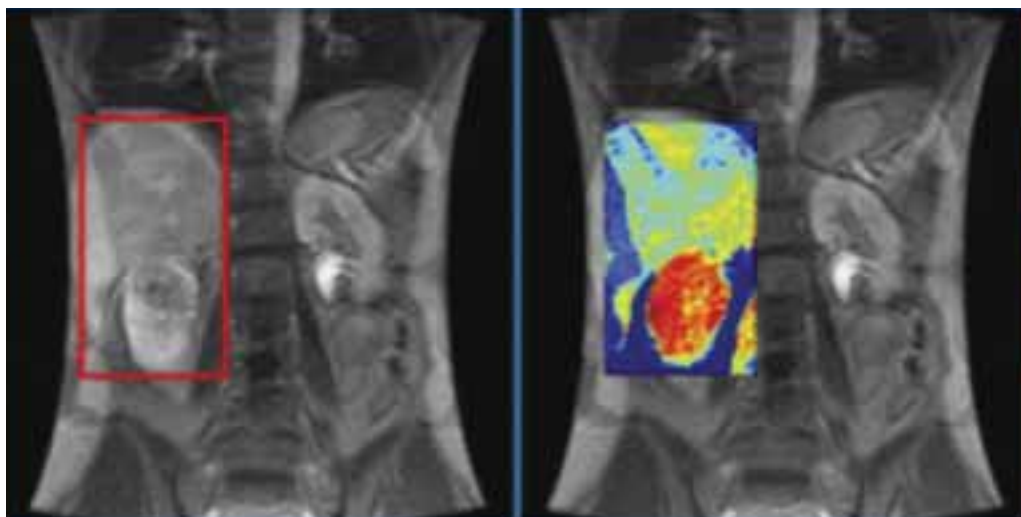
Figure 1: Perfusion MRI. Coronal T1-weighted MRI (left) and Dynamic contrast-enhanced (DCE) MRI (right) of a right renal mass. 3D perfusion parametric map was obtained showing the micro-circulation of the mass. Red color indicates a high level of perfusion. Pathology revealed clear cell RCC, Fuhrman grade 4. Reproduced from Wu et al. with permission.[37]

Figure 2: Diffusion Weighted MRI. Axial DWI (left) and ADC (right) images of the same right renal mass with a b value of 800 s/mm2. On DWI, the high-grade clear cell RCC appears hyperintense, showing restricted diffusion, while the ADC map shows hypointensity, confirming this finding. Reproduced from Wu et al. with permission.[37]

of RCC, including chromophobe. Oncocytoma is often indistinguish- able from chromophobe RCC and this imaging modality may provide a way to avoid surgery and/or biopsy when the preoperative suspicion for oncocytoma is high. Sun et al. used DCE MRI to retrospectively examine the enhancement patterns of pathology-proven clear cell, papillary, and chromophobe RCCs masses. They concluded that each subtype has a characteristic signal intensity change, and this allowed, for example, distinguishing ccRCC from papillary RCC with a 93% sensitivity and 96% specificity.[39] However, the overall applicability of both ASL and DCE MRI to a SRM needs further validation, as neither of the two discussed studies provided T1a subgroup analysis nor relevant statistics such as positive and negative predictive value.

Diffusion MRI reflects random thermal motion of water molecules and can be used to detect and characterize diffusion restricting lesions (**Figure 2**).[37] Diffusion weighted imaging (DWI) with Apparent Diffusion Coefficient (ADC) map can be obtained using a diffusion weighted sequence with a b factor.[40] Images acquired with a low b factor have higher signal to noise ratio and perform well in lesion detection, whereas images acquired with a higher b factor have better contrast and perform better in lesion characterization.

Wang et al. retrospectively evaluated 85 renal masses imaged with DWI and assessed the ability of ADCs to predict RCC subtype.[41] The findings showed that a high b value (of 800 sec/mm2) allowed statistically significant differentiation of clear cell, papillary, and chromophobic RCCs. Further, ccRCC could be differentiated from non-ccRCC with high sensitivity (95.9%) and specificity (94.4%), suggesting that DWI could possibly be a useful modality for preoperative characterization of a SRM. Limitations include the retrospective nature of the study, median mass size of 4.4cm, and absence of T1a subgroup data. Similarly, Taouli et al. retrospectively analyzed 109 renal lesions with DWI and concluded that imaging based

ceptibility Contrast (DSC) and Arterial Spin Labeling (ASL). The former two require the administration of a gadolinium-based contrast agent, while ASL uses blood as an endogenous contrast material. Using corresponding imaging protocols and post-processing techniques,[36] various perfusion parameters, such as transfer constant (Ktrans), blood flow, and blood volume, can be obtained.

Perfusion MRI has been applied in the characterization of renal masses, providing histologic information such as subtype and grade of tumor (**Figure 1**).[37] For instance, Lanzman et al. prospectively obtained preoperative ASL MRI scans in 34 patients with renal masses and compared the results to the postoperative histopathology.[38] Notably, their results showed that oncocytomas demonstrate both higher peak and mean levels of perfusion than all types

diagnosis of solid RCC versus oncocytoma can be accomplished with an area under the curve of 0.85442.

In contrast to the work of Wang et al. and Taouli et al., a retrospective study by Sandrasegaran et al. using DWI for characterization of renal masses had differing results. With a sample size of 42 patients, preoperative ADC measurements of renal masses (using a b value of 800 sec/mm2) were compared to postoperative pathology.[43] The ADC values of the benign cystic lesions were significantly higher than those of the cystic malignant lesions, suggesting that this modality may help reliably differentiate between malignant and non-malignant cysts. The study did not detect a significant difference in ADC values between the different RCC subtypes or tumor grade.

Radiomics

Radiomics is an emerging form of automated image analysis that acquires large amounts of data from images in order to make quantitative decisions about defined tumor regions.[37] The underlying hypothesis is that tumor genomic and proteomic heterogeneity is expressed as intra-tumoral heterogeneity on imaging.[44] Thus, this type of quantitative analysis has the potential to non-invasively predict tumor phenotypes. Gaing et al. performed heterogeneity analysis (mean, standard deviation, skewness and kurtosis) of intravoxel incoherent motion imaging (IVIM) parameters (perfusion fraction (fp), tissue diffusivity (Dt), and pseudodiffusivity (Dp) from DWI MRI preoperatively performed on 44 patients with histopathology proven renal cell carcinomas.[45] They reported that IVIM parameters fp and Dt differentiated 8 of 15 subtype pairs of renal tumors, while histogram analysis differentiated 9 of 15 subtype pairs. These results demonstrate that histogram analysis of IVIM parameters may add complementary value to routine MRI measurements and is a feasible way of distinguishing between renal subtypes.

Conclusions

A number of topics related to kidney cancer imaging are evolving or lack consensus answers and are of great contemporary interest to the field of urology. Safely obtaining contrast-enhanced imaging in patients with renal insufficiency is a topic that plagues all clinicians, though there are a number of proven interventions to ameliorate the risk of CIN. Surveillance protocols are currently stage based, though more sophisticated models employing clinical, pathologic, and genetic variables offer promise for better risk stratification. Finally, novel imaging techniques such as molecular imaging, perfusion/diffusion MRI, and radiomics show great promise in revealing histologic diagnosis of tumors.

Funding

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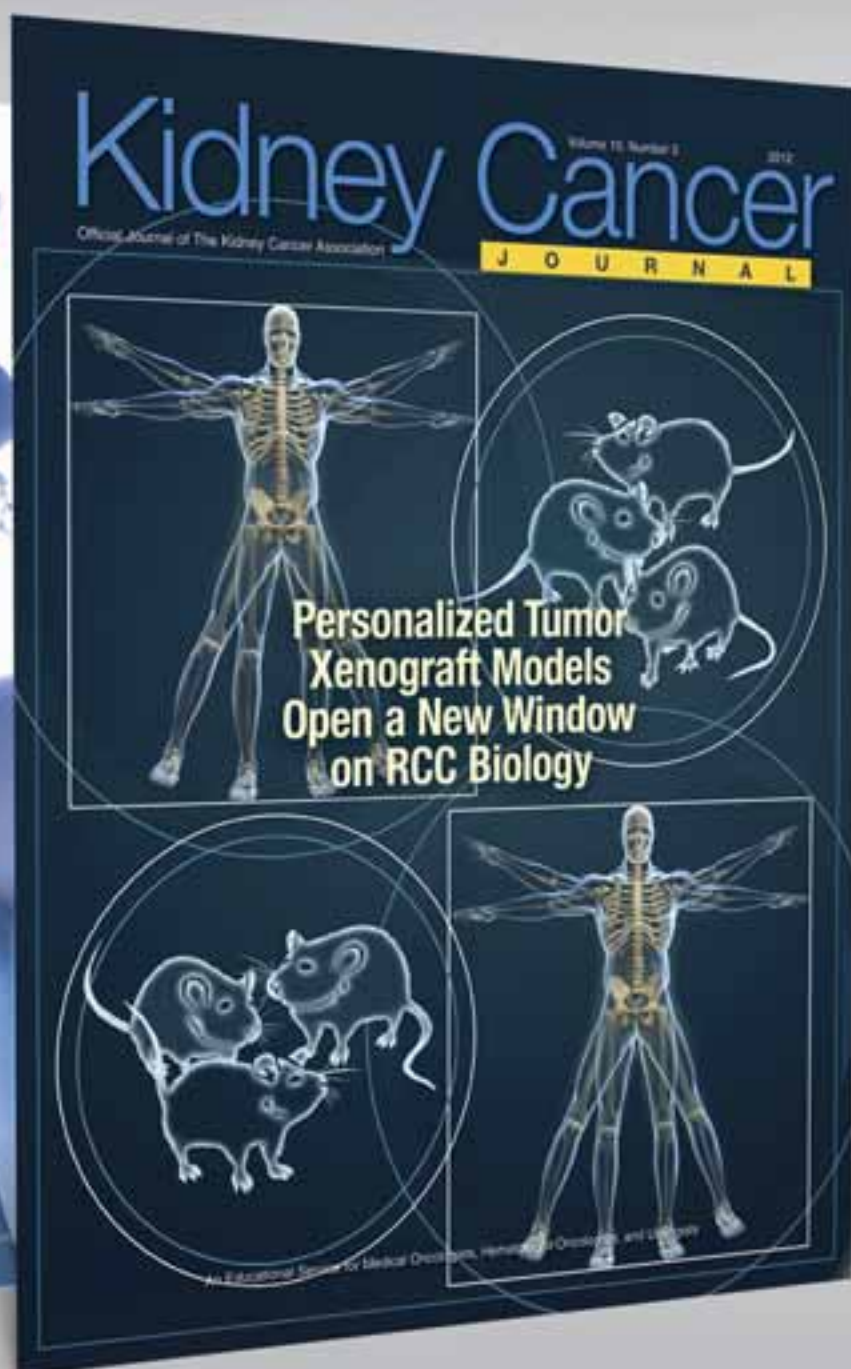
While published response rates are encouraging, how many are durable when immune checkpoint blockade is discontinued? In melanoma patients, the survival curve for patients treated with CTLA-4 blockade (ipilimumab) begins to plateau at 2 years at over 20%, even though the treatment may only last 12 weeks. But emerging evidence suggests that the plateau in the OS curve may not be as firm with PD-1 blockade. For example, in melanoma patients treated with nivolumab, the overall survival rate at 2 years was an impressive 48%, and yet, when patients are followed further, the OS rate trended downward, leading to the question, where will the curve plateau? Identifying the patients who can stop therapy early and those that need maintenance will be essential to improving outcomes for our patients.

During this important discussion at the IKCA meeting, questions that are the subject of ongoing translational research efforts arose, including: What are the mechanisms of innate resistance to PD-1 pathway blockade and what factors, in addition to PD-L1 expression, can reliably predict durable benefit? Preliminary correlative studies were presented that demonstrate that while PD-L1 expression on the tumor or infiltrating immune cells may increase the likelihood of benefit with PD-1 blockade, it fails to reliably identify all responders.

Accumulating evidence was presented that suggests that responsiveness to immune checkpoint blockade may correlate with infiltration of cytotoxic T-cells, tumor grade and mutational/neo-antigen burden. Tumor heterogeneity, which complicates most predictive biomarker discovery efforts in RCC, will almost certainly pose a challenge to investigators. Given the robust antitumor activity of VEGF pathway inhibitors, the application of single agent PD-1 blockade in the treatment naïve setting will likely require the development of a biomarker model that incorporates multiple factors and provides greater positive predictive value.

While many patients do not respond to single agent immunotherapy, the tolerability of these agents makes them ideal backbones for combination treatment regimens designed to overcome resistance. For example, combined inhibition of both CTLA-4 and PD-1 induces impressive antitumor activity, albeit with significant toxicity, in patients with melanoma and is being explored in ccRCC (e.g. NCT02231749). With this approach, tumor responses seem to occur with equal frequency in PD-L1 positive and negative tumors suggesting that the addition of anti-CTLA-4 alters factors in the tumor microenvironment, making PD-L1 negative tumors more susceptible to anti-PD-1 blockade.

Given their additive toxicity and cost, combination approaches need to be rationally designed and used. Pre-clinical models suggest that several other methods of modifying the tumor microenvironment (e.g. binding VEGF, blocking IDO or inhibiting MDSC) enhance the activity of PD-1 pathway blockade, supporting their exploration in randomized trials (e.g. NCT02420821).

Over the last decade, an improved understanding of kidney cancer tumor biology has led to major advancements in the treatment of patients with metastatic disease. While agents that target the VEGF and mTOR pathways prolong survival, resistance develops for most patients within the first year of therapy. Agents that lead to durable remissions are of urgent need to patients living with this disease. To optimize the therapeutic potential of PD-1 blockade, integrated studies that combine clinico-pathologic assessment, genomics, immunology and immunocompetent murine models of kidney cancer will be essential. Emerging data from ongoing basic and translational research studies should help answer many of the important questions that remain.

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stratification. Genomic analysis suggests that the single-nucleotide polymorphism may affect an enhancer region located in the coding region of MET. Further biological mechanistic interrogation is currently underway.

Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicenter trial.
Motzer RJ, Hutson TE, Glen H, et al. *Lancet Oncol.* 2015 Nov;16(15):1473-82. doi: 10.1016/S1470-2045(15)00290-9.

Summary: This study assessed lenvatinib, everolimus, or their combination as second-line treatment in patients with metastatic RCC. It was a randomized, phase 2, open-label, multicenter trial at 37 centers in five countries and enrolled patients with advanced or metastatic, clear-cell RCC. It included patients who had received treatment with a VEGF-targeted therapy and progressed on or within 9 months of stopping that agent. Patients were randomized via an interactive voice response system in a 1:1:1 ratio to either lenvatinib (24 mg/day), everolimus (10 mg/day), or lenvatinib plus everolimus (18 mg/day and 5 mg/day, respectively) administered orally in continuous 28-day cycles until disease progression or unacceptable toxic effects. The primary objective was progression-free survival in the intention-to-treat population; 153 patients were randomly allocated to receive either the combination of lenvatinib plus everolimus (n=51), single agent lenvatinib (n=52), or single-agent everolimus (n=50). Lenvatinib plus everolimus significantly prolonged PFS compared with everolimus alone (median 14·6 months vs 5·5 months *P*=0·0005), but not compared with lenvatinib alone (7·4 months; *P*=0·12). Single-agent lenvatinib significantly prolonged PFS compared with everolimus alone; *P*=0·048). Grade 3 and 4 events occurred in fewer patients allocated single-agent everolimus (25 [50%]) compared with those assigned lenvatinib alone (41 [79%]) or lenvatinib plus everolimus (36 [71%]). The most common grade 3 or 4 treatment-emergent adverse event in patients allocated lenvatinib plus everolimus was diarrhea (ten [20%]), in those assigned single-agent lenvatinib it was proteinuria (ten [19%]), and in those assigned single-agent everolimus it was anemia (six [12%]). Two deaths were deemed related to study drug, one cerebral hemorrhage in the lenvatinib plus everolimus group and one myocardial infarction with single-agent lenvatinib.
Conclusion: Lenvatinib plus everolimus and lenvatinib alone resulted in PFS benefit for patients with metastatic RCC who have progressed after one previous VEGF-targeted therapy. Further study of lenvatinib is warranted in patients with metastatic RCC.

Comprehensive Molecular Characterization of Papillary Renal-Cell Carcinoma.
Linehan WM, Spellman PT, Ricketts CJ, et al. *N Engl J Med.* 2015 Nov 4. Epub ahead of print.

Summary: Papillary RCC, which accounts for 15 to 20% of renal-cell carcinomas, is a heterogeneous disease that consists of various types of renal cancer, including tumors with indolent, multifocal presentation and solitary tumors with an aggressive, highly lethal phenotype. Little is known about the genetic basis of sporadic papillary renal-cell carcinoma, and no effective forms of therapy for advanced disease exist. A comprehensive molecular characterization of 161 primary papillary RCCs was done, using whole-exome sequencing, copy-number analysis, messenger RNA and microRNA sequencing, DNA-methylation analysis, and proteomic analysis. Type 1 and type 2 papillary renal-cell carcinomas were shown to be different types of renal cancer characterized by specific genetic alterations, with type 2 further classified into three individual subgroups on the basis of molecular differences associated with patient survival. Type 1 tumors were associated with MET alterations, whereas type 2 tumors were characterized by CDKN2A silencing, SETD2 mutations, TFE3 fusions, and increased expression of the NRF2-antioxidant response element (ARE) pathway. A CpG island methylator phenotype (CIMP) was observed in a distinct subgroup of type 2 papillary renal-cell carcinomas that was characterized by poor survival and mutation of the gene encoding fumarate hydratase (FH).
Conclusion: Type 1 and type 2 papillary RCCs were shown to be clinically and biologically distinct. Alterations in the MET pathway were associated with type 1, and activation of the NRF2-ARE pathway was associated with type 2; CDKN2A loss and CIMP in type 2 conveyed a poor prognosis. Furthermore, type 2 papillary RCC consisted of at least three subtypes based on molecular and phenotypic features. KCJ

Variant Histology RCC

Chromophobe RCC. *BAP1* and *PBRM1* are infrequently mutated in non-clear cell RCC. Insights were provided into the how the spectrum of diverse genomic alterations can help define non-clear cell RCC subtypes. Payal Kapur, MD from University of Texas Southwestern Medical Center elucidated some of the characteristics of classic chromophobe RCC, which accounts for 5% of all RCC.

This session identified the three main subgroups of renal oncocytic neoplasms—renal oncocytoma, eosinophilic chromophobe RCC, and classic chromophobe RCC. Chromophobe RCCs in general tended to have a lower rate of somatic mutations compared to other RCCs. In addition, eosinophilic chromophobe RCC had different copy number alterations when compared with classic chromophobe RCC. Dr Kapur outlined the extent to which mutations in *TP53* and *PTEN*, the two most common gene mutations in chromophobe RCC, portend worse outcomes in this patient group. In addition, *TP53* mutations tend to be associated with larger tumor size and more advanced stage of disease. However, rather than being considered completely distinct entities, the three subgroups of renal oncocytic neoplasms should be considered a spectrum of disease, with subtle morphologic distinctions between them.

Papillary RCC. The Cancer Genome Atlas (TCGA) Papillary RCC (KIRP) Analysis has provided important perspectives on the molecular-based findings of this cancer. Papillary RCC (PRCC), is the second most common type of RCC and is a heterogeneous disease: the 2 most commonly implicated mutations involve the MET protooncogene and TCA cycle enzyme fumarate hydratase gene.

Information presented by Chad Creighton, PhD from Baylor College of Medicine (which coincided with the online first publication of the KIRP manuscript by TCGA in the *New England Journal of Medicine*), illuminated some of the histology underlying PRCC with implications for further study. Multiplatform analysis (whole exome DNA sequencing, DNA copy number alterations, mRNA expression, miRNA expression, DNA methylation and RPPA), for example, has now identified four distinct subtypes of PRCC (instead of the more traditional type 1 and type 2 based on histology). This analysis revealed differences in overall survival among these 4 groups, with worse survival in patients with the CpG Island Methylator Phenotype (CIMP). One of the key findings was the widespread molecular difference between Type 1 and Type 2 PRCC, as seen in aggregated results from multiple molecular data platforms. Type 2, for example, represents a heterogeneous group of at least three different disease states. Still to be explored is how various pathways could be inhibited, including MET, Hippo, NRF2-ARE since these look like the most promising targets.

Collecting Duct Carcinoma. Reports in the last two years have provided more information on the natural history of collecting duct RCC, but there is a long way to go before genetic and epigenetic drivers of the disease are better understood. There have been only about 400 cases reported in the literature. CDC represents a lethal subtype of RCC which often present at an advanced stage with up to 54% of cases showing metastatic spread at initial presentation, according to data from Gabriel Malouf, MD, PhD from Pitié-Salpêtrière Hospital. Overall survival is estimated to be less than one year in the metastatic setting and the efficacy of targeted agents is generally poor.

Information discussed in this presentation showed that CDC displays a unique gene expression pattern as compared to upper-tract urothelial carcinomas, renal cell carcinomas, and bladder urothelial carcinomas. Up-regulated genes in CDC are related to response to wounding and activation of the immune system. As such, targeting immune checkpoints and/or TFG-pathway might represent new avenues for patients in this setting, but international collaborative studies are urged to better understand this very rare disease.

RCC with Sarcomatoid Dedifferentiation (sRCC). sRCC is a very aggressive entity that constitutes around 5% of all RCCs. More than two thirds of patients generally present with metastatic disease, with a median overall survival of less than a year, even with the advent of targeted therapies.

Jose Karam, MD, from The University of Texas MD Anderson Cancer Center presented an overview of sRCC, including past research as well as ongoing research on the use of imaging and biopsy to preoperatively identify sRCC. In addition, data on characterization of sRCC on the RNA (using RNAseq), DNA (using targeted sequencing, whole exome sequencing and copy number alterations) and protein level (using immunohistochemistry) were presented-all published or ongoing research in 2015-indicating a great interest in further understanding this aggressive disease.

Immunotherapy
[Editor's note: Please see the Guest Editor's Memo for highlights from the meeting with respect to immunotherapy in RCC.]

Emerging Targeted Therapies in RCC
As Thomas E. Hutson, DO, PharmD, reported in his presentation, patients are arriving at the clinic demanding immuno-oncology therapy. However, clinicians need to be aware that there are other therapies clearly poised to shape the therapeutic landscape and alter the treatment paradigm as well. Among the agents and combinations to watch:

- Exciting information is emerging on cabozantinib and it is expected to receive regulatory approval in 2016 based on positive results published in the *New England*

Journal of Medicine in late 2015. The drug has shown a significant PFS advantage in patients who have been previously exposed to one VEGF inhibitor (Final OS results are still awaited). Toxicity appears to be manageable reasonably well.

- An eagerly awaited combination is dalantercept (inhibitor of ALK1 signaling) and axitinib. The PFS of 8.3 months is greater than either drug used alone and without adding significant toxicity. The second phase of the DART study (randomized Phase 2) is currently recruiting and randomizing patients (who were failed by first line therapy) to receive dalantercept+axitinib or placebo+axitinib.

- Back in the picture is tivozanib, a TKI with unique biochemical properties. In the original trial, PFS of patients treated with tivozanib was 11 months, with overall survival of 21.6 months. As a very selective agent, it will be reevaluated after the FDA recommended changes in the criteria for a phase 3 trial in a comparison with sorafenib. The new trial will include patients who were failed by 2 prior therapies (i.e. third-line setting) and randomize them to tivozanib or sorafenib, with primary endpoint of PFS.

- Another combination has also attracted wide interest—lenvatinib, a VEGFR and fibroblast growth factor receptor inhibitor, along with everolimus—in patients who have had disease progression after one prior therapy. This combination has shown a PFS of 14.6 months, greater than either agent when used alone. The overall survival seen so far is in the area of 25.5 months.

Overall, these trials involving targeted treatments could set the stage for a sharp impact on options available, particularly in patients who have been refractory to first-line agents. The panoply of drugs under study have shown remarkable benefit in the second and third line setting and could have an impact on how the paradigm of treatment will change over the next one to two years. **KCJ**

MEDICAL INTELLIGENCE

that we have completed enrollment and look forward to the results."

"Completing enrollment in this Phase 2 trial marks a significant milestone for the company," stated Christopher D. T. Guiffre, President and Chief Executive Officer of Cerulean. "We are grateful for the dedication demonstrated by the patients and the clinical investigators that are participating in this trial."

The Phase 2 trial compares CRLX101 in combination with Avastin to investigator's choice of standard of care in patients with RCC who have received two or three prior lines of therapy. The primary endpoint is investigator-assessed progression free survival (PFS) according to Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1. PFS also will be evaluated by blinded independent radiological review. Other secondary endpoints include overall response rate, duration of response and overall survival. The trial is sized to show a 2.3 month improvement over an expected 3.5 month median PFS for standard of care with a hazard ratio of 0.6, meaning that the trial is expected to show whether CRLX101 plus Avastin provides a 40% improvement in PFS over available third- and fourth-line treatments.

CRLX101 is a nanoparticle-drug conjugate (NDC) designed to concentrate in tumors and slowly release its anti-cancer payload, camptothecin, inside tumor cells. CRLX101 inhibits topoisomerase 1 (topo 1), which is involved in cellular replication, and also inhibits hypoxia-inducible factor-1α (HIF-1α), which research suggests is a master regulator of cancer cell survival mechanisms. CRLX101 has shown activity in four different tumor types, both as monotherapy and in combination with other cancer treatments. CRLX101 is in Phase 2 clinical development and has been dosed in more than 300 patients. The FDA has granted CRLX101 Orphan Drug designation for the treatment of ovarian cancer and Fast Track designation in combination with Avastin in metastatic RCC.

CRLX101, has several properties that make it unique, says Guiffre. A so-called nanoparticle-drug conjugate, it consists of a known cancer-killing agent called camptothecin encapsulated in a molecular shell. The particle is exactly the right size to fit through tiny holes in the walls of new blood vessels — those formed inside tumors — but not through more mature vessels in the rest of the body. The same approach has been taken by other biotech firms (including Bind Therapeutics), but Cerulean's version links the two components together such that the effects are spread out over a longer duration. **KCJ**

2 OUT OF 3

aRCC PATIENTS have hyperactive mTOR*†[1]

> ## How are you addressing potential mTOR hyperactivation in your aRCC patients after failure of sunitinib or sorafenib?

- mTOR is a rational target in aRCC[1]

- AFINITOR® (everolimus) Tablets is an mTOR inhibitor as demonstrated in in vitro/in vivo studies[2]

  *66% (86/130) of metastatic clear cell RCCs obtained from Canadian and US patients. Not based on response.
  †Based on analysis of primary tumor tissues and metastatic lesions (not overall response).

AFINITOR is indicated for the treatment of adults with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib.

Important Safety Information

AFINITOR is contraindicated in patients with hypersensitivity to everolimus, to other rapamycin derivatives, or to any of the excipients.

Noninfectious Pneumonitis

- Noninfectious pneumonitis was reported in up to 19% of patients treated with AFINITOR. The incidence of Common Terminology Criteria (CTC) grade 3 and 4 noninfectious pneumonitis was up to 4.0% and up to 0.2%, respectively. Fatal outcomes have been observed. Monitor for clinical symptoms or radiological changes. Opportunistic infections such as *Pneumocystis jiroveci* pneumonia (PJP) should be considered in the differential diagnosis

- Manage noninfectious pneumonitis by dose interruption until symptoms resolve, follow with a dose reduction, and consider the use of corticosteroids. Discontinue AFINITOR if toxicity recurs at grade 3 or for grade 4 cases

- For patients who require use of corticosteroids, prophylaxis for PJP may be considered

- The development of pneumonitis has been reported even at a reduced dose

aRCC, advanced renal cell carcinoma; mTOR, mammalian target of rapamycin; VEGFR-TKI, vascular endothelial growth factor receptor tyrosine kinase inhibitor.

Approximately

80%

of aRCC PATIENTS
DO NOT receive
>2 lines of therapy[3,4]

> **What do you consider for your aRCC patients after failure of a VEGFR-TKI (sunitinib or sorafenib)?**
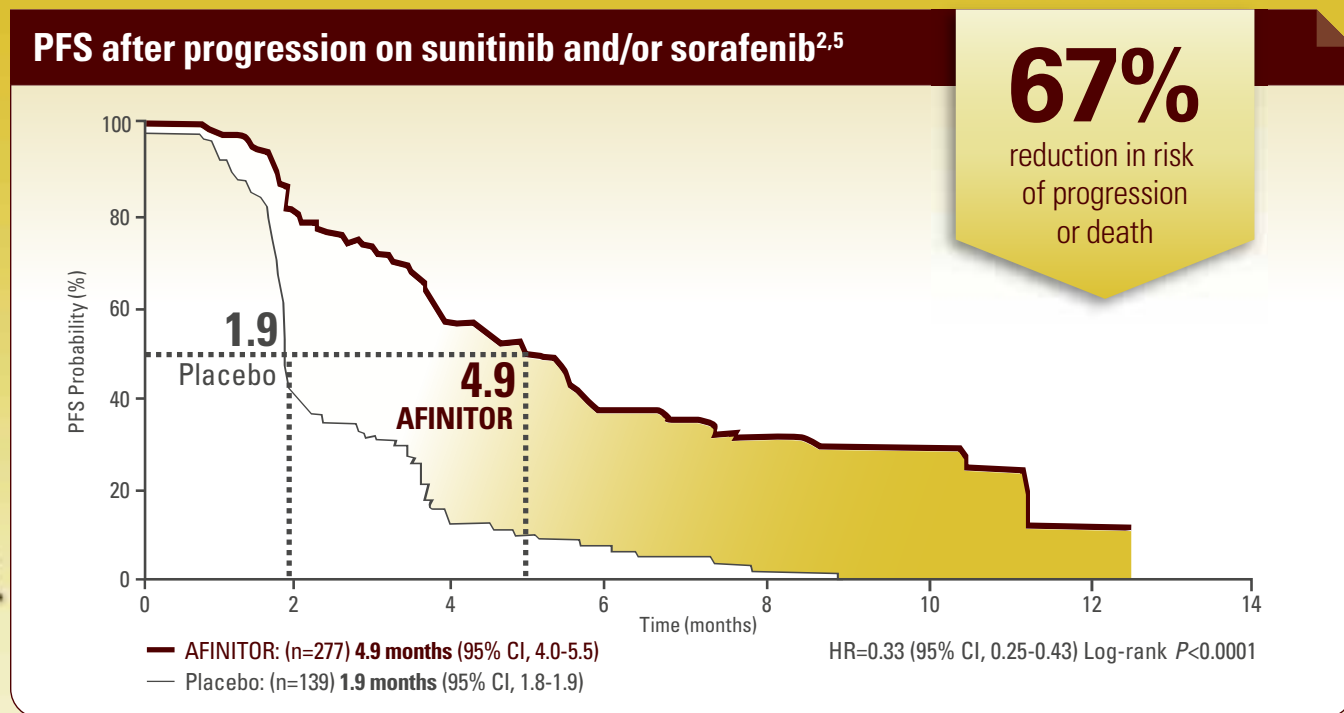
Important Safety Information (cont)

Infections

- AFINITOR has immunosuppressive properties and may predispose patients to bacterial, fungal, viral, or protozoal infections (including those with opportunistic pathogens)
- Localized and systemic infections, including pneumonia, mycobacterial infections, other bacterial infections; invasive fungal infections such as aspergillosis, candidiasis, or PJP; and viral infections, including reactivation of hepatitis B virus, have occurred. Some of these infections have been severe (eg, leading to sepsis, respiratory failure, or hepatic failure) or fatal
- Physicians and patients should be aware of the increased risk of infection with AFINITOR. Treatment of preexisting invasive fungal infections should be completed prior to starting treatment with AFINITOR
- Be vigilant for signs and symptoms of infection and institute appropriate treatment promptly; interruption or discontinuation of AFINITOR should be considered. Discontinue AFINITOR if invasive systemic fungal infection is diagnosed and institute appropriate antifungal treatment
- PJP has been reported in patients who received everolimus, sometimes with a fatal outcome. This may be associated with concomitant use of corticosteroids or other immunosuppressive agents; consider prophylaxis for PJP when concomitant use of these agents is required

Please see additional full Important Safety Information and Brief Summary of Prescribing Information on adjacent pages.

AFINITOR®
(everolimus) tablets

2.5mg | 5mg | 7.5mg | 10mg

AFINITOR® (everolimus) Tablets more than doubled median PFS compared to placebo after progression on a VEGFR-TKI (sunitinib and/or sorafenib)[2,5]

PFS after progression on sunitinib and/or sorafenib[2,5]

67% reduction in risk of progression or death

AFINITOR: (n=277) **4.9 months** (95% CI, 4.0-5.5)
Placebo: (n=139) **1.9 months** (95% CI, 1.8-1.9)

HR=0.33 (95% CI, 0.25-0.43) Log-rank *P*<0.0001

RECORD-1 was an international, multicenter, randomized, double-blind trial comparing AFINITOR 10 mg daily and placebo, both in conjunction with best supportive care, in patients with metastatic RCC whose disease had progressed despite prior treatment with sunitinib, sorafenib, or both sequentially. Prior therapy with bevacizumab, interleukin 2, or interferon-α was also permitted.[2]

Prescribe AFINITOR with confidence

- Every patient in RECORD-1 received a prior VEGFR-TKI (sunitinib and/or sorafenib)[2]
  - 74% had received 1 prior VEGFR-TKI (sunitinib or sorafenib); 26% had received 2 prior VEGFR-TKIs (sunitinib and sorafenib)[2]

Important Safety Information (cont)

- The most common adverse reactions (incidence ≥30%) were stomatitis (44%), infections (37%), asthenia (33%), fatigue (31%), cough (30%), and diarrhea (30%)
- The most common grade 3/4 adverse reactions (incidence ≥5%) were infections (10%), dyspnea (7%), stomatitis (5%), and fatigue (5%)

CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

References: 1. Abou Youssif T, Fahmy MA, Koumakpayi IH, et al. The mammalian target of rapamycin pathway is widely activated without PTEN deletion in renal cell carcinoma metastases. *Cancer.* 2011;117(2):290-300. **2.** AFINITOR [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2015. **3.** Jonasch E, Signorovitch JE, Lin PL, et al. Treatment patterns in metastatic renal cell carcinoma: a retrospective review of medical records from US community oncology practices. *Curr Med Res Opin.* 2014;30(10): 2041-2050. **4.** Harrison MR, George DJ, Walker MS, et al. "Real world" treatment of metastatic renal cell carcinoma in a joint community-academic cohort: progression-free survival over three lines of therapy. *Clin Genitourin Cancer.* 2013;11(4):441-450. **5.** Motzer RJ, Escudier B, Oudard S, et al. Phase 3 trial of everolimus for metastatic renal cell carcinoma. *Cancer.* 2010;116(18):4256-4265.

Please see additional full Important Safety Information and Brief Summary of Prescribing Information on adjacent pages.

Important Safety Information

AFINITOR® (everolimus) Tablets is contraindicated in patients with hypersensitivity to everolimus, to other rapamycin derivatives, or to any of the excipients.

Noninfectious Pneumonitis

- Noninfectious pneumonitis was reported in up to 19% of patients treated with AFINITOR. The incidence of Common Terminology Criteria (CTC) grade 3 and 4 noninfectious pneumonitis was up to 4.0% and up to 0.2%, respectively. Fatal outcomes have been observed. Monitor for clinical symptoms or radiological changes. Opportunistic infections such as *Pneumocystis jiroveci* pneumonia (PJP) should be considered in the differential diagnosis
- Manage noninfectious pneumonitis by dose interruption until symptoms resolve, follow with a dose reduction, and consider the use of corticosteroids. Discontinue AFINITOR if toxicity recurs at grade 3 or for grade 4 cases
- For patients who require use of corticosteroids, prophylaxis for PJP may be considered
- The development of pneumonitis has been reported even at a reduced dose

Infections

- AFINITOR has immunosuppressive properties and may predispose patients to bacterial, fungal, viral, or protozoal infections (including those with opportunistic pathogens)
- Localized and systemic infections, including pneumonia, mycobacterial infections, other bacterial infections; invasive fungal infections such as aspergillosis, candidiasis, or PJP; and viral infections, including reactivation of hepatitis B virus, have occurred. Some of these infections have been severe (eg, leading to sepsis, respiratory failure, or hepatic failure) or fatal
- Physicians and patients should be aware of the increased risk of infection with AFINITOR. Treatment of preexisting invasive fungal infections should be completed prior to starting treatment with AFINITOR
- Be vigilant for signs and symptoms of infection and institute appropriate treatment promptly; interruption or discontinuation of AFINITOR should be considered. Discontinue AFINITOR if invasive systemic fungal infection is diagnosed and institute appropriate antifungal treatment
- PJP has been reported in patients who received everolimus, sometimes with a fatal outcome. This may be associated with concomitant use of corticosteroids or other immunosuppressive agents; consider prophylaxis for PJP when concomitant use of these agents is required

Angioedema With Concomitant Use of Angiotensin-Converting Enzyme (ACE) Inhibitors

- Patients taking concomitant ACE inhibitor therapy may be at increased risk for angioedema (eg, swelling of the airways or tongue, with or without respiratory impairment). In a pooled analysis, the incidence of angioedema in patients taking everolimus with an ACE inhibitor was 6.8% compared to 1.3% in the control arm with an ACE inhibitor

Oral Ulceration

- Mouth ulcers, stomatitis, and oral mucositis have occurred in patients treated with AFINITOR at an incidence ranging from 44% to 78% across the clinical trial experience. Grade 3/4 stomatitis was reported in 4% to 9% of patients
- In such cases, topical treatments are recommended, but alcohol-, hydrogen peroxide-, iodine-, or thyme-containing mouthwashes should be avoided. Antifungal agents should not be used unless fungal infection has been diagnosed

Renal Failure

- Cases of renal failure (including acute renal failure), some with a fatal outcome, have been observed in patients treated with AFINITOR

Impaired Wound Healing

- Everolimus delays wound healing and increases the occurrence of wound-related complications like wound dehiscence, wound infection, incisional hernia, lymphocele, and seroma. These wound-related complications may require surgical intervention. Exercise caution with the use of AFINITOR in the perisurgical period

Laboratory Tests and Monitoring

- Elevations of serum creatinine and proteinuria have been reported. Renal function (including measurement of blood urea nitrogen, urinary protein, or serum creatinine) should be evaluated prior to treatment and periodically thereafter, particularly in patients who have additional risk factors that may further impair renal function
- Hyperglycemia, hyperlipidemia, and hypertriglyceridemia have been reported. Blood glucose and lipids should be evaluated prior to treatment and periodically thereafter. More frequent monitoring is recommended when AFINITOR is coadministered with other drugs that may induce hyperglycemia. Management with appropriate medical therapy is recommended. When possible, optimal glucose and lipid control should be achieved before starting a patient on AFINITOR
- Reductions in hemoglobin, lymphocytes, neutrophils, and platelets have been reported. Monitoring of complete blood count is recommended prior to treatment and periodically thereafter

Drug-Drug Interactions

- Avoid coadministration with strong CYP3A4/PgP inhibitors (eg, ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole)
- Use caution and reduce the AFINITOR dose to 2.5 mg daily if coadministration with a moderate CYP3A4/PgP inhibitor is required (eg, amprenavir, fosamprenavir, aprepitant, erythromycin, fluconazole, verapamil, diltiazem)
- Avoid coadministration with strong CYP3A4/PgP inducers (eg, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital); however, if coadministration is required, consider doubling the daily dose of AFINITOR using increments of 5 mg or less

Hepatic Impairment

- Exposure to everolimus was increased in patients with hepatic impairment. For patients with severe hepatic impairment (Child-Pugh class C), AFINITOR may be used at a reduced dose if the desired benefit outweighs the risk. For patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment, a dose reduction is recommended

Vaccinations

- The use of live vaccines and close contact with those who have received live vaccines should be avoided during treatment with AFINITOR

Embryo-Fetal Toxicity

- Fetal harm can occur if AFINITOR is administered to a pregnant woman. Advise female patients of reproductive potential to use highly effective contraception while using AFINITOR and for up to 8 weeks after ending treatment

Adverse Reactions

- The most common adverse reactions (incidence ≥30%) were stomatitis (44%), infections (37%), asthenia (33%), fatigue (31%), cough (30%), and diarrhea (30%)
- The most common grade 3/4 adverse reactions (incidence ≥5%) were infections (10%), dyspnea (7%), stomatitis (5%), and fatigue (5%)

Laboratory Abnormalities

- The most common laboratory abnormalities (incidence ≥50%, all grades) were: decreased hemoglobin (92%) and lymphocytes (51%); and increased cholesterol (77%), triglycerides (73%), glucose (57%), and creatinine (50%)
- The most common grade 3/4 laboratory abnormalities (incidence ≥5%) were decreased hemoglobin (13%), lymphocytes (18%), and phosphate (6%), and increased glucose (16%)

AFINITOR®
(everolimus) tablets
2.5mg | 5mg | 7.5mg | 10mg

AFINITOR® (everolimus) tablets for oral administration
AFINITOR® DISPERZ (everolimus tablets for oral administration)
Initial U.S. Approval: 2009
BRIEF SUMMARY: Please see package insert for full prescribing information.

1 INDICATIONS AND USAGE

AFINITOR® is indicated for the treatment of adult patients with advanced renal cell carcinoma (RCC) after failure of treatment with sunitinib or sorafenib.

4 CONTRAINDICATIONS

AFINITOR is contraindicated in patients with hypersensitivity to the active substance, to other rapamycin derivatives, or to any of the excipients. Hypersensitivity reactions manifested by symptoms including, but not limited to, anaphylaxis, dyspnea, flushing, chest pain, or angioedema (e.g., swelling of the airways or tongue, with or without respiratory impairment) have been observed with everolimus and other rapamycin derivatives.

5 WARNINGS AND PRECAUTIONS

5.1 Non-infectious Pneumonitis

Non-infectious pneumonitis is a class effect of rapamycin derivatives, including AFINITOR. Non-infectious pneumonitis was reported in up to 19% of patients treated with AFINITOR in clinical trials. The incidence of Common Terminology Criteria (CTC) Grade 3 and 4 non-infectious pneumonitis was up to 4.0% and up to 0.2%, respectively *[see Adverse Reactions (6.1, 6.2, 6.3, 6.4, 6.5) in the full prescribing information]*. Fatal outcomes have been observed.

Consider a diagnosis of non-infectious pneumonitis in patients presenting with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough, or dyspnea, and in whom infectious, neoplastic, and other causes have been excluded by means of appropriate investigations. Opportunistic infections such as pneumocystis jiroveci pneumonia (PJP) should be considered in the differential diagnosis. Advise patients to report promptly any new or worsening respiratory symptoms.

Patients who develop radiological changes suggestive of non-infectious pneumonitis and have few or no symptoms may continue AFINITOR therapy without dose alteration. Imaging appears to overestimate the incidence of clinical pneumonitis.

If symptoms are moderate, consider interrupting therapy until symptoms improve. The use of corticosteroids may be indicated. AFINITOR may be reintroduced at a daily dose approximately 50% lower than the dose previously administered *[see Table 1 in Dosage and Administration (2.2) in the full prescribing information]*.

For cases of Grade 3 non-infectious pneumonitis interrupt AFINITOR until resolution to less than or equal to Grade 1. AFINITOR may be re-introduced at a daily dose approximately 50% lower than the dose previously administered depending on the individual clinical circumstances *[see Dosage and Administration (2.2) in the full prescribing information]*. If toxicity recurs at Grade 3, consider discontinuation of AFINITOR. For cases of Grade 4 non-infectious pneumonitis, discontinue AFINITOR. Corticosteroids may be indicated until clinical symptoms resolve. For patients who require use of corticosteroids for treatment of non-infectious pneumonitis, prophylaxis for PJP may be considered. The development of pneumonitis has been reported even at a reduced dose.

5.2 Infections

AFINITOR has immunosuppressive properties and may predispose patients to bacterial, fungal, viral, or protozoal infections, including infections with opportunistic pathogens *[see Adverse Reactions (6.1, 6.2, 6.3, 6.4, 6.5) in the full prescribing information]*. Localized and systemic infections, including pneumonia, mycobacterial infections, other bacterial infections, invasive fungal infections, such as aspergillosis, candidiasis, or pneumocystis jiroveci pneumonia (PJP) and viral infections including reactivation of hepatitis B virus have occurred in patients taking AFINITOR. Some of these infections have been severe (e.g., leading to sepsis, respiratory or hepatic failure) or fatal. Physicians and patients should be aware of the increased risk of infection with AFINITOR. Complete treatment of pre-existing invasive fungal infections prior to starting treatment with AFINITOR. While taking AFINITOR, be vigilant for signs and symptoms of infection; if a diagnosis of an infection is made, institute appropriate treatment promptly and consider interruption or discontinuation of AFINITOR. If a diagnosis of invasive systemic fungal infection is made, discontinue AFINITOR and treat with appropriate antifungal therapy.

Pneumocystis jiroveci pneumonia, some with a fatal outcome, has been reported in patients who received everolimus. This may be associated with concomitant use of corticosteroids or other immunosuppressive agents. Prophylaxis for PJP should be considered when concomitant use of corticosteroids or other immunosuppressive agents are required.

5.3 Angioedema with Concomitant Use of Angiotensin-Converting Enzyme (ACE) Inhibitors

Patients taking concomitant ACE inhibitor therapy may be at increased risk for angioedema (e.g., swelling of the airways or tongue, with or without respiratory impairment). In a pooled analysis of randomized double-blind oncology clinical trials, the incidence of angioedema in patients taking everolimus with an ACE inhibitor was 6.8% compared to 1.3% in the control arm with an ACE inhibitor.

5.4 Oral Ulceration

Mouth ulcers, stomatitis, and oral mucositis have occurred in patients treated with AFINITOR at an incidence ranging from 44%-78% across the clinical trial experience. Grade 3 or 4 stomatitis was reported in 4%-9% of patients *[see Adverse Reactions (6.1, 6.2, 6.3, 6.4, 6.5) in the full prescribing information]*. In such cases, topical treatments are recommended, but alcohol-, hydrogen peroxide-, iodine-, or thyme- containing mouthwashes should be avoided as they may exacerbate the condition. Antifungal agents should not be used unless fungal infection has been diagnosed *[see Drug Interactions (7.1)]*.

5.5 Renal Failure

Cases of renal failure (including acute renal failure), some with a fatal outcome, have been observed in patients treated with AFINITOR *[see Laboratory Tests and Monitoring (5.8)]*.

5.6 Impaired Wound Healing

Everolimus delays wound healing and increases the occurrence of wound-related complications like wound dehiscence, wound infection, incisional hernia, lymphocele, and seroma. These wound-related complications may require surgical intervention. Exercise caution with the use of AFINITOR in the peri-surgical period.

5.8 Laboratory Tests and Monitoring

Renal Function
Elevations of serum creatinine and proteinuria have been reported in patients taking AFINITOR *[see Adverse Reactions (6.1, 6.2, 6.3, 6.4, 6.5) in the full prescribing information]*. Monitoring of renal function, including measurement of blood urea nitrogen (BUN), urinary protein, or serum creatinine, is recommended prior to the start of AFINITOR therapy and periodically thereafter. Renal function of patients should be monitored particularly where patients have additional risk factors that may further impair renal function.

Blood Glucose and Lipids
Hyperglycemia, hyperlipidemia, and hypertriglyceridemia have been reported in patients taking AFINITOR *[see Adverse Reactions (6.1, 6.2, 6.3, 6.4, 6.5) in the full prescribing information]*. Monitoring of fasting serum glucose and lipid profile is recommended prior to the start of AFINITOR therapy and periodically thereafter as well as management with appropriate medical therapy. More frequent monitoring is recommended when AFINITOR is co-administered with other drugs that may induce hyperglycemia. When possible, optimal glucose and lipid control should be achieved before starting a patient on AFINITOR.

Hematologic Parameters
Decreased hemoglobin, lymphocytes, neutrophils, and platelets have been reported in patients taking AFINITOR *[see Adverse Reactions (6.1, 6.2, 6.3, 6.4, 6.5) in the full prescribing information]*. Monitoring of complete blood count is recommended prior to the start of AFINITOR therapy and periodically thereafter.

5.9 Drug-drug Interactions

Due to significant increases in exposure of everolimus, co-administration with strong CYP3A4/PgP inhibitors should be avoided *[see Dosage and Administration (2.2, 2.5) in the full prescribing information and Drug Interactions (7.1)]*.

A reduction of the AFINITOR dose is recommended when co-administered with a moderate CYP3A4/PgP inhibitor *[see Dosage and Administration (2.2, 2.5) in the full prescribing information and Drug Interactions (7.1)]*.

An increase in the AFINITOR dose is recommended when co-administered with a strong CYP3A4/PgP inducer *[see Dosage and Administration (2.2, 2.5) in the full prescribing information and Drug Interactions (7.2)]*.

5.10 Hepatic Impairment

Exposure to everolimus was increased in patients with hepatic impairment *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

For advanced RCC, with severe hepatic impairment (Child-Pugh class C), AFINITOR may be used at a reduced dose if the desired benefit outweighs the risk. For patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment, a dose reduction is recommended *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3) in the full prescribing information]*.

5.11 Vaccinations

During AFINITOR treatment, avoid the use of live vaccines and avoid close contact with individuals who have received live vaccines (e.g., intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines).

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in another section of the label *[see Warnings and Precautions (5)]*:
- Non-infectious pneumonitis *[see Warnings and Precautions (5.1)]*.
- Infections *[see Warnings and Precautions (5.2)]*.
- Angioedema with concomitant use of ACE inhibitors *[see Warnings and Precautions (5.3)]*.
- Oral ulceration *[see Warnings and Precautions (5.4)]*.
- Renal failure *[see Warnings and Precautions (5.5)]*.
- Impaired wound healing *[see Warnings and Precautions (5.6)]*.

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

6.3 Clinical Study Experience in Advanced Renal Cell Carcinoma

The data described below reflect exposure to AFINITOR (n=274) and placebo (n=137) in a randomized, controlled trial in patients with metastatic renal cell carcinoma who received prior treatment with sunitinib and/or sorafenib. The median age of patients was 61 years (range 27-85), 88% were Caucasian, and 78% were male. The median duration of blinded study treatment was 141 days (range 19-451 days) for patients receiving AFINITOR and 60 days (range 21-295 days) for those receiving placebo.

The most common adverse reactions (incidence ≥ 30%) were stomatitis, infections, asthenia, fatigue, cough, and diarrhea. The most common Grade 3-4 adverse reactions (incidence ≥ 3%) were infections, dyspnea, fatigue, stomatitis, dehydration, pneumonitis, abdominal pain, and asthenia. The most common laboratory abnormalities (incidence ≥ 50%) were anemia, hypercholesterolemia, hypertriglyceridemia, hyperglycemia, lymphopenia, and increased creatinine. The most common Grade 3-4 laboratory abnormalities (incidence ≥ 3%) were lymphopenia, hyperglycemia, anemia, hypophosphatemia, and hypercholesterolemia. Deaths due to acute respiratory failure (0.7%), infection (0.7%), and acute renal failure (0.4%) were observed on the AFINITOR arm but none on the placebo arm. The rates of treatment-emergent adverse events (irrespective of causality) resulting in permanent discontinuation were 14% and 3% for the AFINITOR and placebo treatment groups, respectively. The most common adverse reactions (irrespective of causality) leading to treatment discontinuation were pneumonitis and dyspnea. Infections, stomatitis, and pneumonitis were the most common reasons for treatment delay or dose reduction. The most common medical interventions required during AFINITOR treatment were for infections, anemia, and stomatitis.

Table 6 compares the incidence of treatment-emergent adverse reactions reported with an incidence of ≥ 10% for patients receiving AFINITOR 10 mg daily versus placebo. Within each MedDRA system organ class, the adverse reactions are presented in order of decreasing frequency.

Table 6: Adverse Reactions Reported in at Least 10% of Patients with RCC and at a Higher Rate in the AFINITOR Arm than in the Placebo Arm

	AFINITOR 10 mg/day N=274			Placebo N=137		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Any adverse reaction	97	52	13	93	23	5
Gastrointestinal disorders						
Stomatitis[a]	44	4	<1	8	0	0
Diarrhea	30	1	0	7	0	0
Nausea	26	1	0	19	0	0
Vomiting	20	2	0	12	0	0
Infections and infestations[b]	37	7	3	18	1	0
General disorders and administration site conditions						
Asthenia	33	3	<1	23	4	0
Fatigue	31	5	0	27	3	<1
Edema peripheral	25	<1	0	8	<1	0
Pyrexia	20	<1	0	9	0	0
Mucosal inflammation	19	1	0	1	0	0
Respiratory, thoracic and mediastinal disorders						
Cough	30	<1	0	16	0	0
Dyspnea	24	6	1	15	3	0
Epistaxis	18	0	0	0	0	0
Pneumonitis[c]	14	4	0	0	0	0
Skin and subcutaneous tissue disorders						
Rash	29	1	0	7	0	0
Pruritus	14	<1	0	7	0	0
Dry skin	13	<1	0	5	0	0
Metabolism and nutrition disorders						
Anorexia	25	1	0	14	<1	0
Nervous system disorders						
Headache	19	<1	<1	9	<1	0
Dysgeusia	10	0	0	2	0	0
Musculoskeletal and connective tissue disorders						
Pain in extremity	10	1	0	7	0	0
Median duration of treatment (d)	**141**			**60**		

Grading according to CTCAE Version 3.0
[a] Stomatitis (including aphthous stomatitis), and mouth and tongue ulceration.
[b] Includes all preferred terms within the 'infections and infestations' system organ class, the most common being nasopharyngitis (6%), pneumonia (6%), urinary tract infection (5%), bronchitis (4%), and sinusitis (3%), and also including aspergillosis (<1%), candidiasis (<1%), and sepsis (<1%).
[c] Includes pneumonitis, interstitial lung disease, lung infiltration, pulmonary alveolar hemorrhage, pulmonary toxicity, and alveolitis.

Other notable adverse reactions occurring more frequently with AFINITOR than with placebo, but with an incidence of < 10% include:

Gastrointestinal disorders: Abdominal pain (9%), dry mouth (8%), hemorrhoids (5%), dysphagia (4%)

General disorders and administration site conditions: Weight decreased (9%), chest pain (5%), chills (4%), impaired wound healing (< 1%)

Respiratory, thoracic and mediastinal disorders: Pleural effusion (7%), pharyngolaryngeal pain (4%), rhinorrhea (3%)

Skin and subcutaneous tissue disorders: Hand-foot syndrome (reported as palmar-plantar erythrodysesthesia syndrome) (5%), nail disorder (5%), erythema (4%), onychoclasis (4%), skin lesion (4%), acneiform dermatitis (3%), angioedema (<1%)

Metabolism and nutrition disorders: Exacerbation of pre-existing diabetes mellitus (2%), new onset of diabetes mellitus (< 1%)

Psychiatric disorders: Insomnia (9%)

Nervous system disorders: Dizziness (7%), paresthesia (5%)

Eye disorders: Eyelid edema (4%), conjunctivitis (2%)

Vascular disorders: Hypertension (4%), deep vein thrombosis (< 1%)

Renal and urinary disorders: Renal failure (3%)

Cardiac disorders: Tachycardia (3%), congestive cardiac failure (1%)

Musculoskeletal and connective tissue disorders: Jaw pain (3%)

Hematologic disorders: Hemorrhage (3%)

Key laboratory abnormalities are presented in Table 7.

Table 7: Key Laboratory Abnormalities Reported in Patients with RCC at a Higher Rate in the AFINITOR Arm than the Placebo Arm

Laboratory parameter	AFINITOR 10 mg/day N=274			Placebo N=137		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Hematology[a]						
Hemoglobin decreased	92	12	1	79	5	<1
Lymphocytes decreased	51	16	2	28	5	0
Platelets decreased	23	1	0	2	0	<1
Neutrophils decreased	14	0	<1	4	0	0
Clinical chemistry						
Cholesterol increased	77	4	0	35	0	0
Triglycerides increased	73	<1	0	34	0	0
Glucose increased	57	15	<1	25	1	0
Creatinine increased	50	1	0	34	0	0
Phosphate decreased	37	6	0	8	0	0
Aspartate transaminase (AST) increased	25	<1	<1	7	0	0
Alanine transaminase (ALT) increased	21	1	0	4	0	0
Bilirubin increased	3	<1	<1	2	0	0

Grading according to CTCAE Version 3.0
[a] Reflects corresponding adverse drug reaction reports of anemia, leukopenia, lymphopenia, neutropenia, and thrombocytopenia (collectively pancytopenia), which occurred at lower frequency.

6.6 Postmarketing Experience

The following adverse reactions have been identified during post approval use of AFINITOR. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate frequency or establish a causal relationship to drug exposure: acute pancreatitis, cholecystitis, cholelithiasis, arterial thrombotic events and reflex sympathetic dystrophy.

7 DRUG INTERACTIONS

Everolimus is a substrate of CYP3A4, and also a substrate and moderate inhibitor of the multidrug efflux pump PgP. In vitro, everolimus is a competitive inhibitor of CYP3A4 and a mixed inhibitor of CYP2D6.

7.1 Agents That May Increase Everolimus Blood Concentrations

CYP3A4 Inhibitors and PgP Inhibitors
In healthy subjects, compared to AFINITOR treatment alone there were significant increases in everolimus exposure when AFINITOR was coadministered with:
- ketoconazole (a strong CYP3A4 inhibitor and a PgP inhibitor) - C_{max} and AUC increased by 3.9- and 15.0-fold, respectively.
- erythromycin (a moderate CYP3A4 inhibitor and a PgP inhibitor) - C_{max} and AUC increased by 2.0- and 4.4-fold, respectively.
- verapamil (a moderate CYP3A4 inhibitor and a PgP inhibitor) - C_{max} and AUC increased by 2.3- and 3.5-fold, respectively.

Concomitant strong inhibitors of CYP3A4/PgP should not be used *[see Dosage and Administration (2.2, 2.5) in the full prescribing information and Warnings and Precautions (5.9)]*.

Use caution when AFINITOR is used in combination with moderate CYP3A4/PgP inhibitors. If alternative treatment cannot be administered reduce the AFINITOR dose *[see Dosage and Administration (2.2, 2.5) in the full prescribing information and Warnings and Precautions (5.9)]*.

7.2 Agents That May Decrease Everolimus Blood Concentrations
CYP3A4/PgP Inducers
In healthy subjects, co-administration of AFINITOR with rifampin, a strong inducer of CYP3A4 and an inducer of PgP, decreased everolimus AUC and C_{max} by 63% and 58% respectively, compared to everolimus treatment alone. Consider a dose increase of AFINITOR when co-administered with strong CYP3A4/PgP inducers if alternative treatment cannot be administered. St. John's Wort may decrease everolimus exposure unpredictably and should be avoided *[see Dosage and Administration (2.2, 2.5) in the full prescribing information]*.

7.3 Drugs That May Have Their Plasma Concentrations Altered by Everolimus
Studies in healthy subjects indicate that there are no clinically significant pharmacokinetic interactions between AFINITOR and the HMG-CoA reductase inhibitors atorvastatin (a CYP3A4 substrate) and pravastatin (a non-CYP3A4 substrate) and population pharmacokinetic analyses also detected no influence of simvastatin (a CYP3A4 substrate) on the clearance of AFINITOR.

A study in healthy subjects demonstrated that co-administration of an oral dose of midazolam (sensitive CYP3A4 substrate) with everolimus resulted in a 25% increase in midazolam C_{max} and a 30% increase in midazolam $AUC_{(0-inf)}$.

Coadministration of everolimus and exemestane increased exemestane C_{min} by 45% and C_{2h} by 64%. However, the corresponding estradiol levels at steady state (4 weeks) were not different between the 2 treatment arms. No increase in adverse events related to exemestane was observed in patients with hormone receptor-positive, HER2-negative advanced breast cancer receiving the combination.

Coadministration of everolimus and depot octreotide increased octreotide C_{min} by approximately 50%.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category D

Risk Summary
Based on the mechanism of action, AFINITOR can cause fetal harm when administered to a pregnant woman. Everolimus caused embryo-fetal toxicities in animals at maternal exposures that were lower than human exposures. If this drug is used during pregnancy or if the patient becomes pregnant while taking the drug, apprise the patient of the potential hazard to the fetus *[see Warnings and Precautions (5.12) in the full prescribing information]*.

Animal Data
In animal reproductive studies, oral administration of everolimus to female rats before mating and through organogenesis induced embryo-fetal toxicities, including increased resorption, pre-implantation and post-implantation loss, decreased numbers of live fetuses, malformation (e.g., sternal cleft), and retarded skeletal development. These effects occurred in the absence of maternal toxicities. Embryo-fetal toxicities in rats occurred at doses ≥ 0.1 mg/kg (0.6 mg/m^2) with resulting exposures of approximately 4% of the exposure (AUC_{0-24h}) achieved in patients receiving the 10 mg daily dose of everolimus. In rabbits, embryotoxicity evident as an increase in resorptions occurred at an oral dose of 0.8 mg/kg (9.6 mg/m^2), approximately 1.6 times either the 10 mg daily dose or the median dose administered to SEGA patients on a body surface area basis. The effect in rabbits occurred in the presence of maternal toxicities.

In a pre- and post-natal development study in rats, animals were dosed from implantation through lactation. At the dose of 0.1 mg/kg (0.6 mg/m^2), there were no adverse effects on delivery and lactation or signs of maternal toxicity; however, there were reductions in body weight (up to 9% reduction from the control) and in survival of offspring (~5% died or missing). There were no drug-related effects on the developmental parameters (morphological development, motor activity, learning, or fertility assessment) in the offspring.

8.3 Nursing Mothers
It is not known whether everolimus is excreted in human milk. Everolimus and/or its metabolites passed into the milk of lactating rats at a concentration 3.5 times higher than in maternal serum. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from everolimus, 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.

8.5 Geriatric Use
In two other randomized trials (advanced renal cell carcinoma and advanced neuroendocrine tumors of pancreatic origin), no overall differences in safety or effectiveness were observed between elderly and younger patients.

Other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

No dosage adjustment in initial dosing is required in elderly patients, but close monitoring and appropriate dose adjustments for adverse reactions is recommended *[see Dosage and Administration (2.2), Clinical Pharmacology (12.3) in the full prescribing information]*.

8.6 Females and Males of Reproductive Potential
Contraception
Females
AFINITOR can cause fetal harm when administered to a pregnant woman. Advise female patients of reproductive potential to use highly effective contraception while receiving AFINITOR and for up to 8 weeks after ending treatment *[see Use in Specific Populations (8.1)]*.

Infertility
Females
Menstrual irregularities, secondary amenorrhea, and increases in luteinizing hormone (LH) and follicle stimulating hormone (FSH) occurred in female patients taking AFINITOR. Based on these clinical findings and findings in animals, female fertility may be compromised by treatment with AFINITOR *[see Adverse Reactions (6.2, 6.4, 6.5) and Nonclinical Toxicology (13.1) in the full prescribing information]*.

Males
AFINITOR treatment may impair fertility in male patients based on animal findings *[see Nonclinical Toxicology (13.1) in the full prescribing information]*.

8.7 Renal Impairment
No clinical studies were conducted with AFINITOR in patients with decreased renal function. Renal impairment is not expected to influence drug exposure and no dosage adjustment of everolimus is recommended in patients with renal impairment *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

8.8 Hepatic Impairment
The safety, tolerability and pharmacokinetics of AFINITOR were evaluated in a 34 subject single oral dose study of everolimus in subjects with impaired hepatic function relative to subjects with normal hepatic function. Exposure was increased in patients with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

For advanced RCC, AFINITOR may be used at a reduced dose if the desired benefit outweighs the risk. For patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment, a dose reduction is recommended *[see Dosage and Administration (2.2) in the full prescribing information]*.

10 OVERDOSAGE
In animal studies, everolimus showed a low acute toxic potential. No lethality or severe toxicity was observed in either mice or rats given single oral doses of 2000 mg/kg (limit test).

Reported experience with overdose in humans is very limited. Single doses of up to 70 mg have been administered. The acute toxicity profile observed with the 70 mg dose was consistent with that for the 10 mg dose.

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