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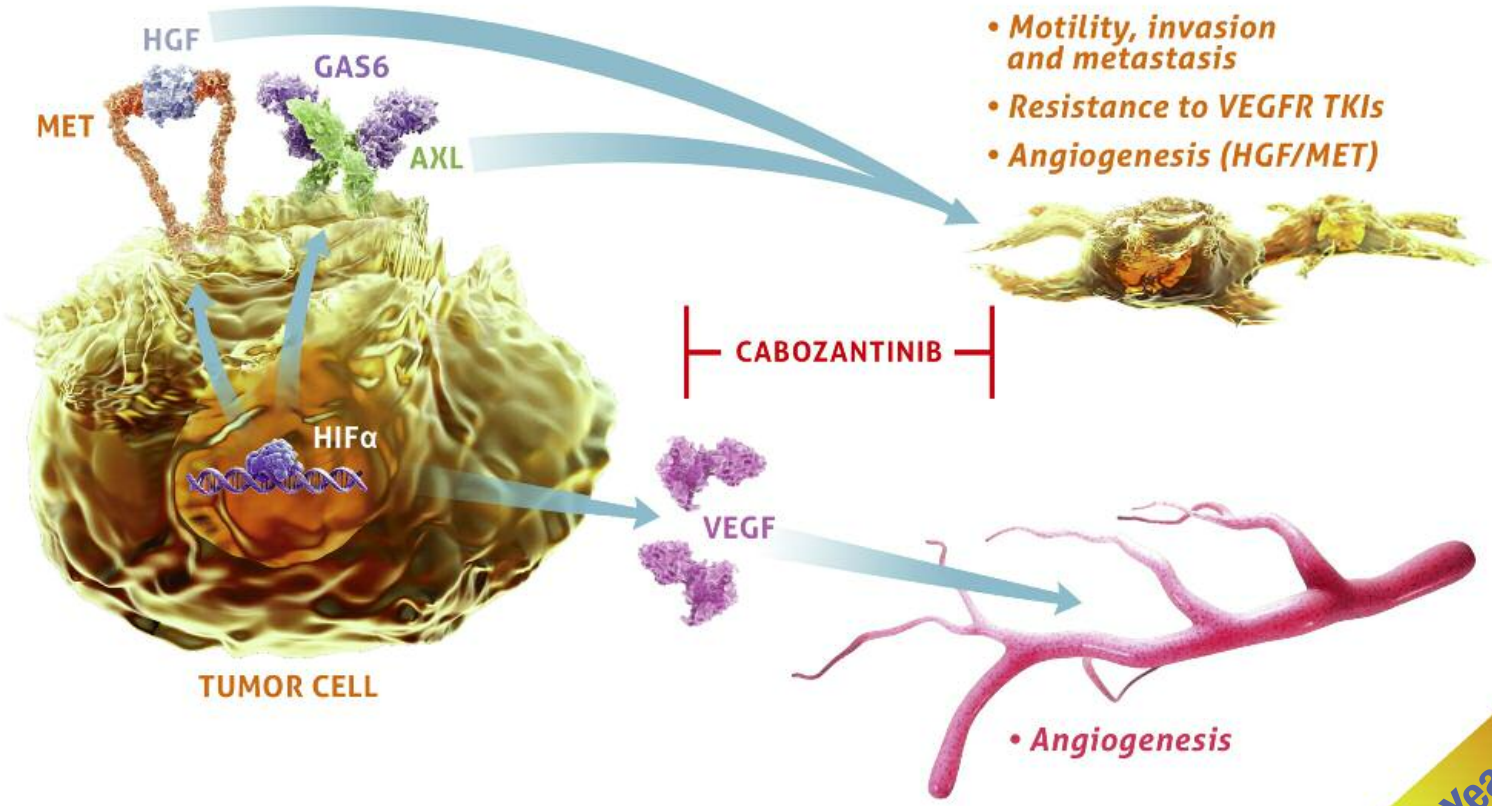
Pivotal Results in Frontline Therapy Point Toward Paradigm Shift, Improved Efficacy

Case Studies: Remote Monitoring of Advanced RCC Patients Could Speed Intervention

Society of Urologic Oncology Meeting Presents Translational Findings



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

Now in Its 16th Year

INLYTA® (axitinib) 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.

Inlyta®
axitinib 1mg and 5mg tablets

Continue the fight with INLYTA

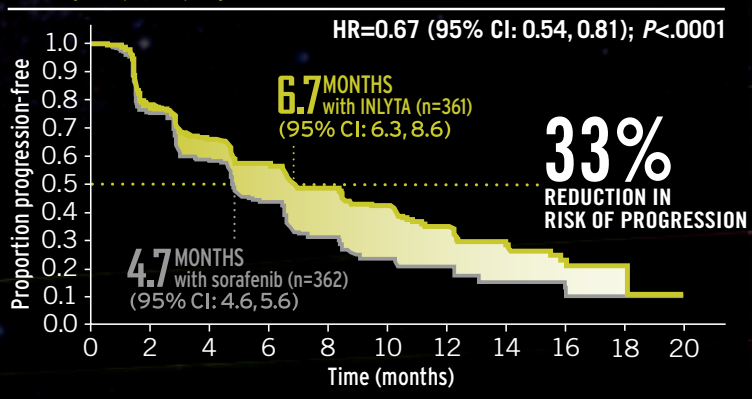
Proven efficacy with a distinct safety profile

The ONLY approved treatment option to demonstrate

Significant and superior PFS vs a VEGFR-TKI in a phase 3 trial for 2nd-line mRCC*

*Based on MEDLINE® literature review for phase 3 trials in mRCC as of November 2016.

Primary endpoint: progression-free survival (PFS)



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

A distinct safety profile

Over 4 years of clinical experience	49,000 patients treated worldwide†	7 clinical studies reported in a long-term safety analysis[2]

†IMS® MIDAS™, July 2016.

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.

November 2016

Pfizer U.S. Pharmaceuticals

References: 1. Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. *Lancet*. 2011;378(9807):1931-1939.
2. Rini BI, Escudier B, Hariharan S, et al. Long-term safety with axitinib in previously treated patients with metastatic renal cell carcinoma. *Clin Genitourin Cancer*. 2015;13(6):540-547.
mRCC=metastatic renal cell carcinoma; TKI=tyrosine kinase inhibitor.

INLYTA® (AXITINIB) TABLETS FOR ORAL ADMINISTRATION
Initial U.S. Approval: 2012

Brief Summary of Prescribing Information

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

DOSAGE AND ADMINISTRATION

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

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

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

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

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

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

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

DOSAGE FORMS AND STRENGTHS

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

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

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DRUG INTERACTIONS

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

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

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

USE IN SPECIFIC POPULATIONS

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

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

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

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

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

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

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

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

No dosage adjustment is required in elderly patients.

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

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

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

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

OVERDOSAGE

There is no specific treatment for INLYTA overdose.

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

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

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

NONCLINICAL TOXICOLOGY

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

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

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

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

PATIENT COUNSELING INFORMATION

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

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

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

Rx only August 2014

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

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About the Cover
Arrows in illustration highight the role of various pathways, AXL, MET and VEGF in tumorigenesis. By inhibiting, AXL and MET, the tyrosine kinase inhibitor, cabozantinib, interrupts a cascade of events leading to angiogenesis. HIF--hypoxia-inducible factor--is also implicated in the process promoting tumor growth. Cabozantinib is among the agents under study as frontline therapy in patients with advanced renal cell carcinoma. Although not depicted here, an immuno-oncology strategy, including the use of combination therapy in the form of ipilimumab and nivolumab, is also proposed as a potential first-line approach.

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KCJ EDITOR'S MEMO

'Future Shock'? Is That Where We Are in Frontline Treatment for RCC?


Robert A. Figlin, MD

When futurist author Alvin Toffler wrote a book in 1970 called *Future Shock*, the title worked its way into the national lexicon as a way to describe how society was reacting to overwhelming technological change. He described it as a personal perception of "too much change in too short a period of time" or simply, information overload where we are struggling, perhaps even stressed, to keep up with the accelerated pace of new information.

Is it a bridge too far to suggest that in some respects our knowledge base in renal cell carcinoma (RCC) has left more than a few observers in "future shock," trying to keep up with the velocity of changes that in 2018 could usher in significant changes in the strategies for frontline therapy in RCC? Perhaps "future shock" is an exaggeration, but it is certainly accurate to envision a time a few months from now, perhaps when we are all preparing for the next ASCO meeting in June, when we look forward to a calculus to help us clarify the multitude of changes proposed for frontline and second line therapy for RCC.

Recent meetings of the European Society of Medical Oncology (ESMO) and other scientific sessions such as the Society for Immunotherapy of Cancer (SITC) suggest a key turning point in frontline strategies for renal cell carcinoma (RCC). We are on the cusp of a shift in the paradigm for frontline choices. Now that cabozantinib has been approved (*see page 103*), and assuming that the ipilimumab-nivolumab combination will be approved in the foreseeable future, there are a wide range of questions that need to be addressed as we grapple with choices in an attempt to apply evidence-based approaches to a shifting paradigm of treatment.

The ESMO meeting of 2017 helped to move the needle on several fronts, notably with regard to data on cabozantinib. With previous data compiled by an open-label design, we needed additional evidence to support the findings from the CABOSUN trial. ESMO delivered what was expected in the form of results from an independent review board. Results from the IRC indicated that the response rate for frontline cabozantinib in intermediate- and poor-risk patients declined, but that is fairly typical of what might be expected.

We know from experience in other trials that when investigators proceed

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Kidney Cancer Journal Author Guidelines

Scope of Manuscripts

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

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

Manuscript Submission

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

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Peer Review and Editing

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

Conflict of Interest

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

Manuscript Preparation

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

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

References

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

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Essential Peer-Reviewed Reading in Kidney Cancer

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

Adjuvant therapy in renal cell carcinoma: does higher risk for recurrence improve the chance for success? **Figlin RA, Leibovich BC, Stewart GD, et al. *Ann Oncol*. 2017 Nov 24; doi: 10.1093/annonc/mdx743.**

Summary: The success of targeted therapies, including inhibitors of the vascular endothelial growth factor pathway or the mammalian target of rapamycin, in the treatment of metastatic renal cell carcinoma (RCC) led to interest in testing their efficacy in the adjuvant setting. Results from the first trials are now available with other studies due to report imminently. This review provides an overview of adjuvant targeted therapy in RCC, including interpretation of currently available conflicting data and future direction of research. It discusses the key differences between the completed targeted therapy adjuvant trials, and highlight the importance of accurately identifying patients who are likely to benefit from adjuvant treatment. Also considered are reasons why blinded independent radiology review and treatment dose may prove critical for adjuvant treatment success. The implications of using disease-free survival as a surrogate endpoint for overall survival from the patient perspective and measurement of health benefit have recently been brought into focus and are discussed. Finally, the paper discusses how the ongoing adjuvant trials with targeted therapies and checkpoint inhibitors may improve our understanding and ability to prevent tumor recurrence after nephrectomy in the future.

Insights into Epigenetic Remodeling in VHL-Deficient Clear Cell Renal Cell Carcinoma. **Ricketts CJ, Linehan WM. *Cancer Discov*. 2017 Nov; 7(11):1221-1223. doi: 10.1158/2159-8290.**

Summary: Clear cell renal cell carcinoma (ccRCC) is characterized by loss of the von Hippel-Lindau tumor suppressor gene (*VHL*), and the functional tumorigenic consequences of this loss have been used to develop therapies for advanced ccRCC, such as targeting activation of the HIF pathway. Yao and colleagues elucidate how VHL loss contributes to chromatin alteration at both gene promoters and enhancers/superenhancers, in both an HIF-dependent as well as independent manner, and how this may provide additional targets for therapeutic intervention in advanced ccRCC.

HIF2 targeted RNAi therapeutic inhibits clear cell renal cell carcinoma. **Wong SC, Cheng W, Hamilton H, et al. *Mol Cancer Ther*. 2017 Oct 27; pii: molcanther. 0471.2017. doi: 10.1158/1535-7163.**

Summary: Targeted therapy against VEGF and mTOR pathways has been established as the standard-of-care for metastatic clear cell renal cell carcinoma (ccRCC); however, these treatments frequently fail and most patients become refractory requiring subsequent alternative therapeutic options. Therefore, development of innovative and effective treatments is imperative. About 80-90% of ccRCC tumors express an inactive mutant form of the von Hippel-Lindau protein (pVHL), an E3 ubiquitin ligase that promotes target protein degradation. Strong genetic and experimental evidence supports the correlate that pVHL functional loss leads to the accumulation of the transcription factor hypoxia-inducible factor 2 (HIF2) and that an over-abundance of HIF2 functions as a tumorigenic driver of ccRCC.

Conclusion: In this report, we describe an RNAi therapeutic for HIF2 that utilizes a targeting ligand that selectively binds to integrins v 3 and v 5 frequently over-expressed in ccRCC. We demonstrate that functional delivery of a HIF2 specific RNAi trigger resulted in HIF2 gene silencing and subsequent tumor growth inhibition and degeneration in an established orthotopic ccRCC xenograft model.

Tumor Microvessel Density as a Prognostic Marker in High-Risk Renal Cell Carcinoma Patients Treated on ECOG-ACRIN E2805. **Jilaveanu LB, Puligandla MA, Weiss SA, et al. *Clin Cancer Res*. 2017 Oct 24; doi: 10.1158/1078-0432.**

Summary: Increased vascularity is a hallmark of renal cell carcinoma (RCC). Microvessel density (MVD) is one measurement of tumorangiogenesis; however, its utility as a biomarker of outcome is unknown. ECOG-ACRIN 2805 (E2805) enrolled 1,943 resected high-risk RCC patients randomized to adjuvant sunitinib, sorafenib, or placebo. We aimed to determine the prognostic and predictive role of MVD in RCC. We obtained pretreatment primary RCC nephrectomy tissues from 822 patients on E2805 and constructed tissue microarrays. Using quantitative immunofluorescence, we measured tumor MVD as the area of CD34- expressing cells. We determined the association with disease-free survival (DFS), overall survival (OS), treatment arm, and clinicopathologic variables. High MVD (above the median) was associated with prolonged OS for the entire cohort ($P = 0.021$) and for patients treated with placebo ($P = 0.028$). The association between high MVD and OS was weaker in patients treated with sunitinib or sorafenib ($P = 0.060$). MVD was not associated with DFS ($P = 1.00$). On multivariable analysis, MVD remained independently associated with improved OS ($P = 0.013$). High

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

FDA Approves Cabozantinib (Cabometyx) Tablets forPreviously Untreated Advanced RCC – *Approval expands indication*

Acting earlier than expected, the FDA has approved cabozantinib tablets for the expanded indication of patients with advanced renal cell carcinoma (RCC). The FDA's priority review and approval was based on results from the randomized phase 2 CABOSUN trial in patients with previously untreated RCC, which demonstrated a statistically significant and clinically meaningful improvement in progression-free survival (PFS) versus sunitinib, a current standard of care. Previously, approval was not expected until February.

The label expansion follows the initial FDA approval of cabozantinib in April 2016 for the treatment of patients with advanced RCC who have previously received anti-angiogenic therapy.

"The CABOSUN trial enrolled treatment-naïve patients with advanced kidney cancer, including those who are known to fare poorly, such as patients with intermediate- or poor-prognostic factors and those with bone metastases or multiple sites of metastatic disease," said Toni Choueiri, MD, a principal investigator on the CABOSUN trial and Director, Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Boston.

"Physicians are already experienced in using CABOMETYX in the second-line advanced RCC setting, and it is a much-needed advance to also now have CABOMETYX as an option for their patients with previously untreated advanced RCC," he added

The expanded approval of the agent is based on results of the phase 2 CABOSUN trial, which met its primary endpoint of improving PFS.

According to the independent radiology review committee analysis of the data, cabozantinib demonstrated a clinically meaningful andstatistically significant 52% reduction in the rate of disease progression or death (HR 0.48, 95% CI 0.31-0.74, *P*=0.0008).

Median PFS for cabozantinib was 8.6 months vs 5.3 months for sunitinib, corresponding to a 3.3 month (62%) improvement. All causality grade 3 or 4 adverse reactions occurred in 68% of patients receiving cabozantinib and 65% of patients receiving sunitinib. The most frequent all causality Grade 3-4 adverse reactions (≥5 percent) in patients treated with canozantinib were hypertension, diarrhea, hyponatremia, hypophosphatemia, palmarplantar erythrodysesthesia (PPE), fatigue, increased ALT, decreased appetite, stomatitis, pain, hypotension, and syncope. Twenty-one percent of patients in the cabozantinib arm compared to 22% of patients receiving sunitinib discontinued treatment due to adverse events.

FDA Approves Adjuvant Sunitinib for High-Risk RCC

The FDA has approved sunitinib (Sutent) for use as an adjuvant therapy in patients with renal cell carcinoma (RCC) who have received nephrectomy and are high risk for recurrence. Approval for sunitinib is based on findings from the phase III S-TRAC trial, which were presented at the 2016 ESMO Congress and published in the *New England Journal of Medicine*. In the study, adjuvant sunitinib prolonged disease-free survival (DFS) by 1.2 years compared with placebo following nephrectomy for patients with high-risk clear cell RCC.

After a median follow-up duration of 5.4 years, the median DFS was 6.8 years in the sunitinib arm compared with 5.6 years with placebo (HR, 0.76; 95% CI, 0.59-0.98; *P* = .03). In higher risk patients, the median DFS was 6.2 versus 4.0 years for sunitinib and placebo, respectively (HR, 0.74; 95% CI, 0.55-0.99; *P* = .04). Grade 3/4 adverse events (AEs) were experienced by 63.4% of patients in the sunitinib group compared with 21.7% in the placebo arm. The FDA approved sunitinib for this indication despite a 6-6 vote on the potential approval from its Oncologic Drugs Advisory Committee in September.

"This is the first adjuvant treatment approved for patients with renal cell carcinoma, which is significant because patients with this disease who have a nephrectomy are often at high risk of the cancer returning," Richard Pazdur, MD, director of the FDA's Oncology Center of Excellence and acting director of the Office of Hematology and Oncology Products in the FDA's Center for Drug Evaluation and Research, said in a statement. "There is now an approved therapy for patients who previously did not have options to potentially reduce cancer recurrence."

The study randomized 615 patients with clear cell RCC to receive sunitinib (n = 309) or placebo (n = 306). Patient characteristics were well balanced between the arms. The median age of patients in the sunitinib arm was 57 years, and most were males (71.8%). Most patients had an ECOG performance score of 0 (73.8%). Overall, 90.6% of those in the sunitinib arm had a stage 3 tumor, with no nodal involvement and no metastasis. Of these patients, 37.2% were considered low-risk (any Fuhrman grade and ECOG score of 0 or Fuhrman grade 1 and ECOG score of ≥1) and 53.4% were high-risk (Fuhrman grade ≥2 and ECOG score of ≥1). Sunitinib was administered at 50 mg daily for 4 weeks followed by 2 weeks without treatment. One dose reduction was allowed in the study, to 37.5 mg per day. Overall, more than half of patients (54.2%) were able to maintain treatment with the starting dose of 50 mg per day. The median daily dose was 45.9 mg.

After 3 years, 64.9% of those in the sunitinib group were alive and remained disease-free compared with 59.5% in the placebo arm. At 5 years, the DFS rate was 59.3% with

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Frontline Strategies in RCC: Capturing Pivotal New Data, Optimizing Treatment Options

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Editor's note: This report by the Kidney Cancer Journal *integrates recently published peer-reviewed medical literature and results presented at two meetings, the European Society of Medical Oncology (ESMO) sessions and the Society for Immunotherapy of Cancer (SITC) meeting, both held in late 2017. The content, compiled independently by the journal, was assessed for accuracy, clarity, and relevance by the three peer reviewers whose investigative work has focused on trends covered in this report.*

Compelling evidence for the approval of two therapies as frontline strategies in intermediate and poor-risk advanced renal cell carcinoma (RCC) has raised expectations that significant improvements in progression-free survival and overall survival are possible with a manageable safety profile in patients previously treated with the conventional antiangiogenic standard of care. Cabozantinib was approved for all first-line RCC patients on December 19, 2017 so it can be considered a new standard of care option. Clinicians can look forward to a broader spectrum of therapy to optimize outcomes, based on results from two pivotal trials analyzed here.

The momentum of two clinical trials has generated expectations and excitement that a realignment of strategies in the first-line treatment of renal cell carcinoma has indeed arrived. For 10 years, the focus of frontline therapy generally has been antiangiogenic agents that target the vascular endothelial growth factor (VEGF) and its receptors, and the blockade of the VEGF signaling pathway has been the standard treatment based on improved clinical outcomes in randomized phase III trials.[1] However, recent results presented at the European Society of Medical Oncology (ESMO) meeting in 2017 suggest how this realignment of strategies may take shape in the coming year as the FDA considers approval of new options for frontline therapy in RCC.

As we look beyond ESMO and attention turns toward further exploration of immunotherapy, including the combination of ipilimumab-nivolumab, and the rationale for using the TKI cabozantinib, there is wide speculation on how the treatment algorithm will change, what special considerations, including PD-L1 status, could be important in selecting appropriate therapy, and how new combinations can be sequenced to achieve optimal outcomes. As much as ESMO helped clarify these choices, it also presented even more challenges and questions still to be addressed as phase III investigations further explore the importance of:

- multi-pathway inhibition involving not only VEGF but also MET and AXL.
- the role of biomarkers such as PD-L1 status and how that could be integrated into assessments to identify patients who may benefit from immune-oncology based treatment.
- the tolerability of various agents
- the presence or absence of bone metastases and other pre-existing conditions, such as autoimmune disease.
- risk status and how that may stratify patients for various treatments, including the use of sunitinib.

Two Therapies and their Mechanisms of Action

Cabozantinib

Cabozantinib (Cabometyx) is a small-molecule inhibitor of the VEGF receptor and, in addition, inhibits MET and AXL, receptors shown to be upregulated in VHL-deficient RCC cells and associated with resistance to VEGF-directed therapy in preclinical RCC models.[1] Furthermore, cabozantinib has been shown to directly inhibit migration and invasion in RCC cell lines that have been stimulated with hepatocyte growth factor, the ligand for MET.[1] Cabozantinib tablets were approved by regulatory authorities on the basis of a randomized phase III trial in patients with

Keywords: renal cell carcinoma, intermediate and poor risk-patients, cabozantinib, CABOSUN, Checkmate214, ipilimumab, nivolumab, AXL, MET, sunitinib, standard of care, progression-free survival, overall survival.

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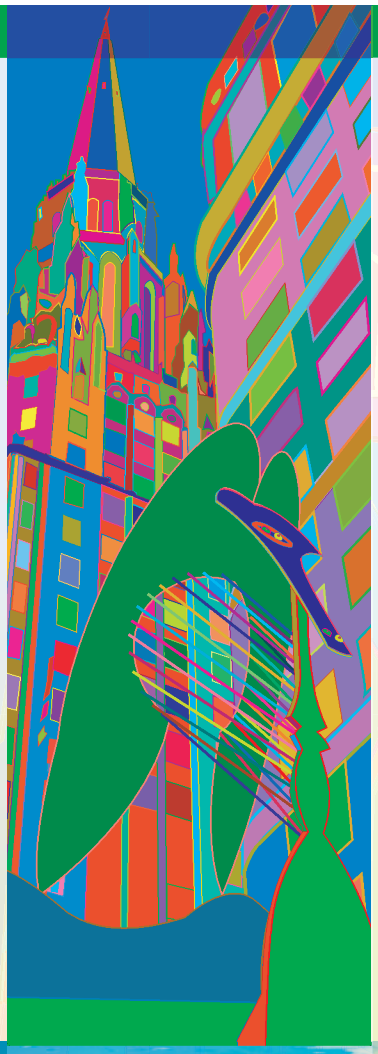

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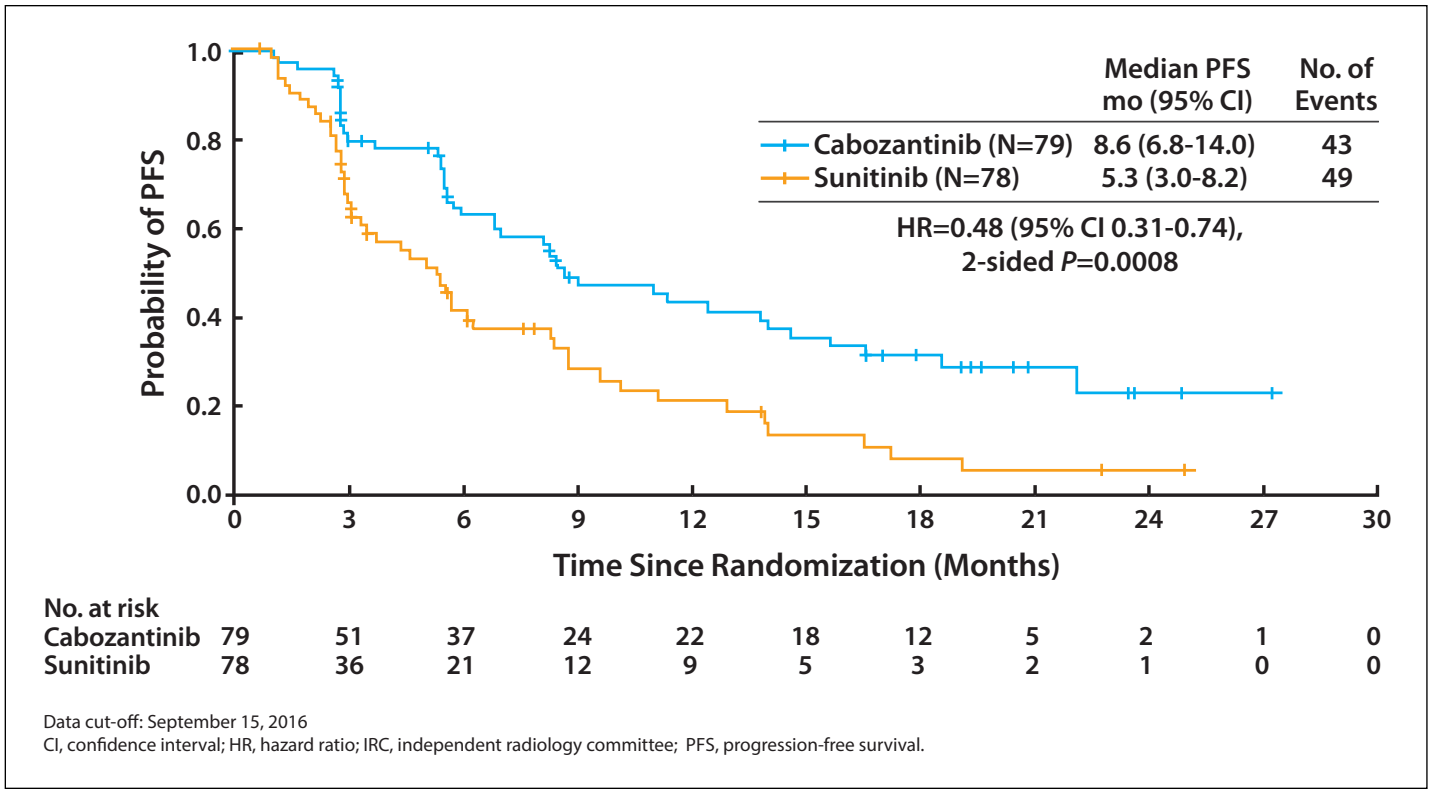


Data cut-off: September 15, 2016
CI, confidence interval; HR, hazard ratio; IRC, independent radiology committee; PFS, progression-free survival.

Figure 1. Kaplan-Meier Plot of Progression-Free Survival per IRC.

mRCC previously treated with at least one VEGF-targeted agent, with demonstration of progression-free survival (PFS) and overall survival (OS) benefits compared with a mammalian target of rapamycin inhibitor, everolimus, which was commonly used in the refractory setting.[2] Prior limited prospective data had supported the hypothesis that VEGF targeting would have a greater clinical effect compared with mammalian target of rapamycin inhibition in mRCC.[3] Based on the recent CABOSUN results, Cabometyx has now been approved by the FDA for the treatment of patients with advanced RCC, expanding the label to previously untreated patients.[4]

CABOSUN and the Results at ESMO

If one were looking for significant new data to reframe the debate on frontline treatment of metastatic RCC, CABOSUN produced compelling results at the 2017 ESMO meeting. By significantly extending progression-free survival (PFS) compared with sunitinib as initial targeted therapy for intermediate- and poor-risk patients with metastatic RCC as assessed by an independent radiological review committee, the results extended earlier findings from CABOSUN. (**Figures 1,2**)

In assessing cabozantinib as initial targeted therapy for patients with poor- or intermediate-risk clear-cell metastatic RCC, CABOSUN also:

- Included patients who had a notable number of other independent adverse prognostic risk factors such as a high rate of bone metastases.[5]
- Produced radiographic findings that showed cabozantinib significantly prolonged median PFS compared with sunitinib (8.6 months vs 5.3 months).
- Safety profiles of the drugs appeared to be consistent with prior reports. A comparable percentage of cabozantinib- and sunitinib-treated patients experienced grade 3 or grade 4 adverse events (68% vs 65%).

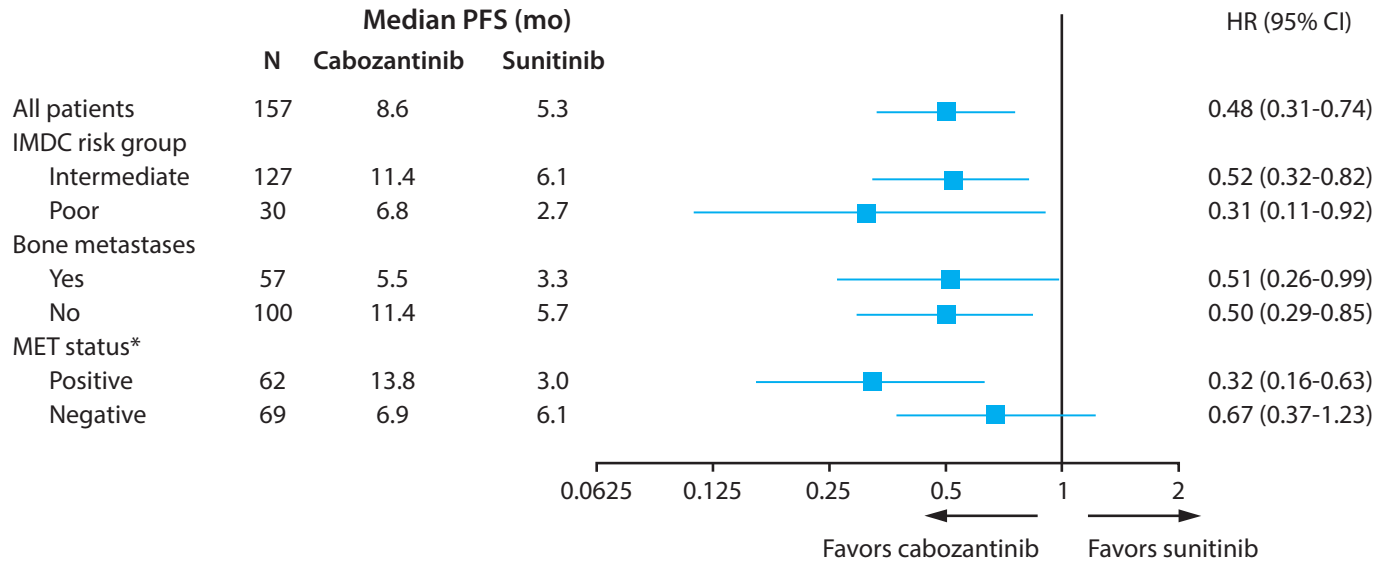
Combination of Ipilimumab and Nivolumab (ipi-nivo)

Nivolumab (Opdivo) is a programmed death-1 (PD-1) immune checkpoint inhibitor that is designed to harness the body's own immune system to help restore anti-tumor immune response. By harnessing the body's own immune system to fight cancer, nivolumab has become an important treatment option across multiple cancers.[6] Nivolumab is indicated for the treatment of patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy.

Ipilimumab (Yervoy) is a monoclonal antibody that works to activate the immune system by targeting CTLA-4, a protein receptor that downregulates the immune system. Cytotoxic T lymphocytes (CTLs) can recognize and destroy cancer cells. However, an inhibitory mechanism interrupts this destruction. Ipilimumab turns off this inhibitory mechanism and allows CTLs to function.[7] Ipilimumab was approved by the FDA in 2011 for the treatment of melanoma.

Checkmate -214: Comparing IO With Sunitinib

CheckMate -214 is a phase 3, randomized, open-label study evaluating the combination of nivolumab plus ipilimumab versus sunitinib in patients with previously untreated advanced or metastatic RCC. Patients in the



*Eight patients in the cabozantinib group and 18 patients in the sunitinib group had unknown MET status.

All randomized patients were included in the analyses. Hazard ratios are unstratified with the the exception of the analysis for all patients.
CI, confidence interval; HR, hazard ratio; IMDC, internationsal metastatic renal cell carcinoma database consortium; IRC, independent radiology committee; mo, months; PFS, progression-free survival.

Figure 2. Forest Plots of Progression-Free Survival per IRC.

combination group received nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks for 4 cycles followed by nivolumab 3 mg/kg every 2 weeks. Patients in the comparator group received sunitinib 50 mg once daily for 4 weeks, followed by 2 weeks off before continuation of treatment. Patients were treated until progression or unacceptable toxic effects.

The primary endpoints of the trial were overall survival (OS), objective response rate (ORR), and progression-free survival (PFS) in an intermediate- to poor-risk patient population (approximately 75% of patients).[8] Safety was a secondary endpoint. The key findings from Checkmate -214 revealed:

- The median overall survival (OS) was not reached with the combination versus 32.9 months with sunitinib (HR, 0.68; 99.8% CI, 0.49-0.95; *P* = .0003). In those specifically with intermediate- and poor-risk RCC, who constituted about 75% of the intent-to-treat (ITT) population, median OS was not reached in the nivolumab and ipilimumab arm and was 26.0 months in the sunitinib arm, a 37% reduction in the risk of death (HR, 0.63; 99.8% CI, 0.44-0.89; *P* <.0001). Overall survival for the combination versus sunitinib in those with favorable risk has not yet been reported. (**Figures 3,4**)
- The overall response rate (ORR) favored the combination over sunitinib in intermediate/poor risk patients irrespective of baseline tumor PD-L1 expression while a PFS benefit with the combination was seen only in patients with PD-L1 ≥1%. (Figure) For the favorable risk group, the sunitinib arm was favored over the combination for PFS and ORR.

Grade 3/4 adverse events (AEs) were reported in 46% of patients (252/547) in the combination group, compared with 63% of patients (337/535) in the sunitinib group. The most common grade 3/4 AEs in the combination group were fatigue (4%), diarrhea (4%), nausea (2%), decreased appetite (1%), and, in less than 1% each, pruritus, hypothyroidism and hypertension. In the sunitinib group, the most common grade 3/4 AEs were hypertension (16%), fatigue (9%), Palmar-plantar erythrodysaesthesia syndrome (9%), diarrhea (5%), stomatitis (3%), mucosal inflammation (3%), nausea (1%), decreased appetite (1%), and in less than 1% each, hypothyroidism and dysgeusia. Adverse events (AEs) leading to discontinuation were reported in 22% of patients (120/547) in the combination group, compared with 12% of patients in the sunitinib group (64/535). Seven treatment-related deaths occurred in the combination group and four in the sunitinib group.

Checkmate -214 delineated the role of PD-L1 expression to a greater extent than has previously been elucidated. Programmed death-ligand 1 (PD-L1) expression level impacted response to nivolumab plus ipilimumab, regardless of risk category. In patients with IMDC intermediate/poor risk and PD-L1 ≥1%, ORR was 53% with nivolumab plus ipilimumab, versus 22% with sunitinib (*P*<.0001). By comparison, if patients with IDMC intermediate/poor risk had PD-L1 <1%, ORR with nivolumab plus ipilimumab was 37%, compared to 22% with sunitinib (*P* = .0252). Results in the ITT population showed that nivolumab plus ipilimumab was associated with a statistically significant improvement in ORR in patients

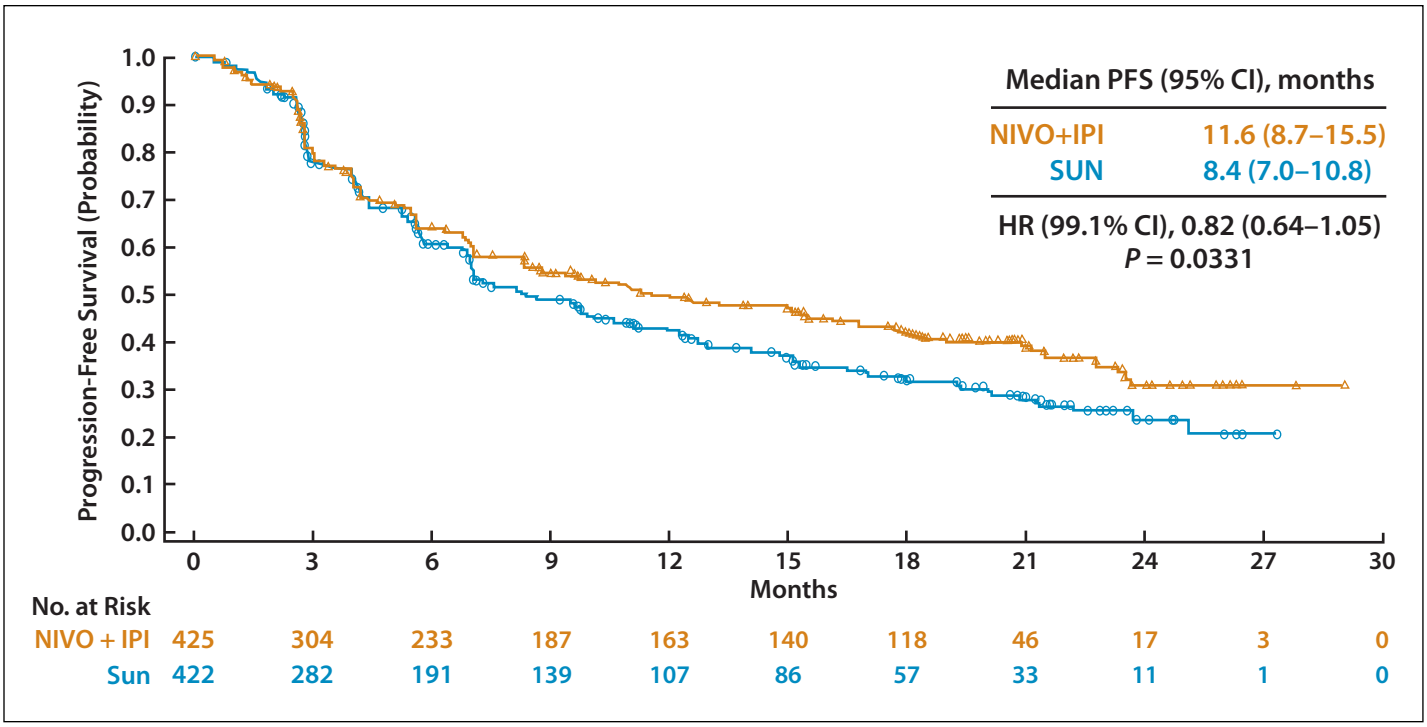


Figure 3. PFS per IRRC: IMDC intermediate/poor risk. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab + ipilimumab vs sunitinib for treatment-naïve advanced or metastatic renal cell carcinoma (RCC): results from CheckMate214, including overall survival by subgroups. Society for Immunotherapy for Cancer 2017 meeting; Abstract 038.

with PD-L1 ≥1% (53% vs 22%; *P*<.0001), but not for patients with PD-L1 <1% (36% vs 35%; *P* = .8799).

Several conclusions were drawn from the CheckMate -214 trial and presented at the SITC meeting. The authors suggested that the combination regimen should be considered as a new standard-of-care option for patients with intermediate/poor risk advanced RCC. The results were considered compelling in view of the OS benefit across PD-L1 expression levels, supporting the use of the combination as an alternative to sunitinib. Additionally, the safety profile of the combination was manageable with patients reporting a better quality of life than with sunitinib.

Interpreting the Data in CABOSUN: Why Was Cabozantinib Superior to Sunitinib?

There are numerous factors potentially at play in determining why cabozantinib is under consideration as frontline therapy based on CABOSUN data and the recent approval of cabozantinib for first-line patients.. As background, one should be aware of what patient groups were selected as part of the trial enrollment process. CABOSUN focused on IMDC intermediate- and poor-risk groups because these groups would capture 70% to 80% of all patients with advanced disease who are the most in need of systemic therapy and disease control, whereas the favorable-risk group includes many patients with relatively indolent, lower-volume disease.[9,10]

The study also included a patient population with a high rate of bone metastases; this is known to be a negative prognostic factor in RCC. With a high percentage of patients with poor risk factors, including bone metastases, enrolled in the CABOSUN trial, this study picked up on an observation from a large French study that showed patients with RCC with bone metastases had a reduced benefit from sunitinib.[11] This was true even when the French group adjusted for known prognostic factors in advanced RCC. There is a trend suggesting cabozantinib is of benefit in this subset, based on additional findings. The phase III METEOR trial, for example, showed a marked improvement in PFS and OS in patients with bone metastases who received cabozantinib compared with everolimus.[12] In CABOSUN, investigators also found a PFS benefit with cabozantinib in all subgroups of patients, including those with bone metastases.

The Target Profile: Can Biomarkers Predict Clinical Activity?

One explanation for the superiority of cabozantinib over sunitinib may be related to the target profile of cabozantinib, which includes the MET and AXL pathways in addition to VEGFR. Efforts to uncover the strength of such an association are ongoing. The HGF/MET pathway has attracted increasing attention in recent years as a promising molecular target for cancer therapy. An improved understanding of the involvement of this pathway in kidney development and in renal pathological conditions has suggested the targeting of this pathway as a promising strategy for the treatment of kidney cancer.

The observation that the kidney is an abundant source of hepatocyte growth factor (HGF) and its activators, may explain, at least in part, why patients with germline *MET*

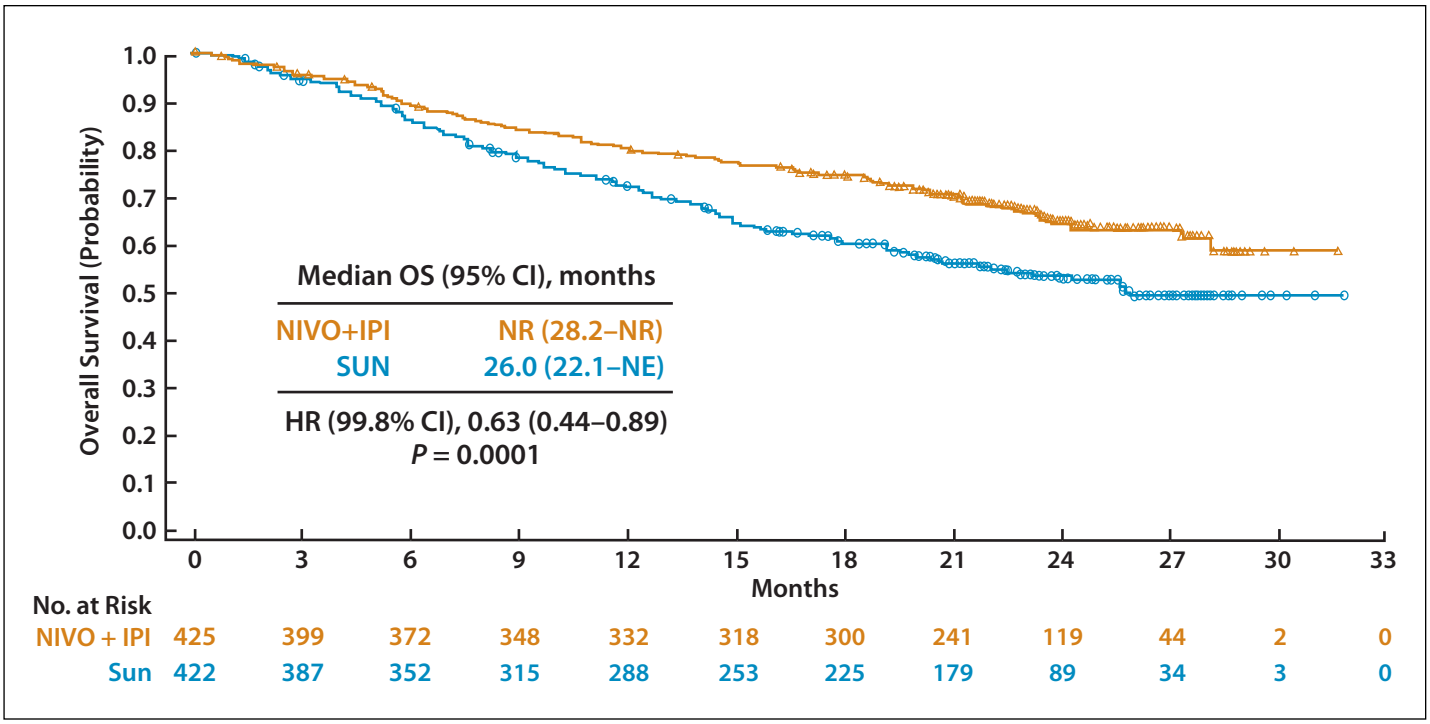


Figure 4. OS: IMDC intermediate/poor risk. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab + ipilimumab vs sunitinib for treatment-naïve advanced or metastatic renal cell carcinoma (RCC): results from CheckMate214, including overall survival by subgroups. Society for Immunotherapy for Cancer 2017 meeting; Abstract 038.

mutations exhibit only kidney cancer.[13] These studies also demonstrated that mutated MET might be more easily activated than wild-type MET and more likely to remain activated for longer periods after stimulation. Although the role of MET expression in tumors was investigated in the METEOR trial it does not appear to be to be predictive of the clinical activity of cabozantinib over everolimus, there is still widespread interest in this possible connection and other blood and tissue biomarkers that could yield clues as to the activity of cabozantinib.[14]

The AXL Pathway and Its Role in RCC

AXL signaling is also implicated in tumor growth and survival. Activation of AXL by its cognate ligand GAS6 promotes cell proliferation, migration, and protection from apoptosis; in many contexts, AXL functions in concert with other receptors to amplify downstream signaling pathways.[15] Despite the success of anti-angiogenic agents in treating RCC, a fraction of patients do not respond to systemic therapy, and responding patients eventually progress and succumb to their disease. Resistance to VEGF-targeted therapy is mediated by upregulation of alternative angiogenic and invasive pathways, including MET and AXL.

Zhou et al hypothesized that sunitinib-induced upregulation of the prometastatic MET and AXL receptors is associated with resistance to sunitinib and with more aggressive tumor behavior.[16] In their study, tissue microarrays containing sunitinib-treated and untreated RCC tissues were stained with MET and AXL antibodies. The low malignant RCC cell line 786-O was chronically treated with sunitinib and assayed for AXL, MET, epithelial-mesenchymal transition (EMT) protein expression and activation. Co-culture experiments were used to examine the effect of sunitinib pretreatment on endothelial cell growth. The effects of AXL and MET were eval- uated in various cell-based models by short hairpin RNA or inhibition by cabozantinib, which targets VEGF, MET and AXL.

Xenograft mouse models tested the ability of cabozantinib to rescue sunitinib resistance. Zhou et al demonstrated that increased AXL and MET expression was associated with inferior clinical outcome in patients. Chronic sunitinib treatment of RCC cell lines activated both AXL and MET, induced EMT-associated gene expression changes, including upregulation of Snail and catenin, and increased cell migration and invasion. Pretreatment with sunitinib enhanced angiogenesis in 786-0/human umbilical vein endothelial cell co-culture models.

The suppression of AXL or MET expression and the inhibition of AXL and MET activation using cabozantinib both impaired chronic sunitinib treatment-induced prometastatic behavior in cell culture and rescued acquired resistance to sunitinib in xenograft models. In summary, chronic sunitinib treatment induces the activation of AXL and MET signaling and promotes prometastatic behavior and angiogenesis. The inhibition of AXL and MET activity may overcome resistance induced by prolonged sunitinib therapy in metastatic RCC. These findings need to be confirmed in further studies elucidating the role of biomarkers in resistance to sunitinib.

But if confirmed, this could represent an important new direction in our ability to assess the prognostic significance of such biomarkers.

Conclusion

Evidence from two pivotal trials comparing new therapeutic approaches as initial therapy for patients with metastatic RCC of poor or intermediate risk to a long standing standard of care sunitinib are likely to have a meaningful impact on the treatment paradigm if one or both of these options is approved, as expected in early 2018. This may mean that for the first time in more than 10 years, the standard of care in these patients, which has been sunitinib, will undergo significant change with the approval of Cabometyx achieved in 2017 and the expected approval of ipi-nivo in 2018.

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Mobile Health Applications in Patients With Metastatic Renal Cell Carcinoma

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Introduction

During the last decade, 10 drugs have been approved by the Food and Drug Administration (FDA) for the treatment of metastatic renal cell carcinoma (mRCC). Many of these treatments are oral tyrosine kinase inhibitors (TKI's) targeting the vascular endothelial growth factor (VEGF) receptor. These TKI's are known to cause a variety of side effects including fatigue, hypertension, nausea, diarrhea, weight loss, palmar-plantar erythrodysesthesia, rash, and endocrine side effects. The exact timing and degree of side effects are difficult to predict but can be serious in 50% or more of cases. Given that these drugs are generally dosed at near maximum tolerated doses in all patients (i.e. flat dosing) and that the toxicities can be rapid onset in some cases within days or weeks of starting therapy, prompt recognition and management of toxicities are crucial to ensure safe management that will still lead to clinical efficacy.[1-3] Other targeted therapies used in the treatment of mRCC include mammalian target of rapamycin (mTOR) inhibitors and immune checkpoint inhibitors, both of which can also have a wide variety of toxicities requiring close monitoring. Current and future indications may include combinations of these agents that further enhance their risks. Therefore, as new cancer therapies and indications for treatment are developed, it is imperative we maximize the ability to monitor patients in real time to assess rapid physiologic changes that could be harbingers of more serious safety concerns.

The mobile health (mHealth) industry is one of the largest growing business sectors in the world.[4] In recent years, smart phone technology has advanced considerably, and patients are able to use a variety of devices to monitor health related parameters including physical activity, diet, blood pressure, heart rate, weight, blood sugar and many other important variables.[4,5] Even prior to the rise of mHealth, telemedicine has been shown to be an effective tool to help manage many chronic medical problems including diabetes, heart failure, COPD and mental health.[6-9] Although mHealth applications are being explored in cancer care,[10,11] there are no published clinical trials evaluating the use of mHealth technology in clinical monitoring of patients with mRCC.

Side effects are quite common with VEGF inhibitor therapy. For instance a pooled analysis of clinical studies of patients treated with the now FDA approved VEGF inhibitors sunitinib, sorafenib, pazopanib, axitinib, and bevacizumab, showed dose reductions in 13-52% of patients, dose interruptions 21-72% of patients, and discontinuations due to adverse events in 4-28% of patients.[12] This is important as failure to maintain dose intensity may lead to decrease in survival in patients with mRCC.[13] Hypertension, a side effect of these drugs was found to occur in 20-40% of patients. Gastrointestinal side effects such as anorexia, nausea, vomiting, and diarrhea were commonly reported in approximately 30-60% of patients and fatigue was reported in 50-60% of cases.[12] Physical activity monitoring may be a valuable tool in assessing functionality in cancer patients and also a potential tool to encourage exercise, which may help combat symptoms like fatigue.[14] As a result, in a very small study, we sought to investigate how mHealth technology could be used to monitor important clinical parameters including blood pressure, weight, and physical activity in patients initiat-

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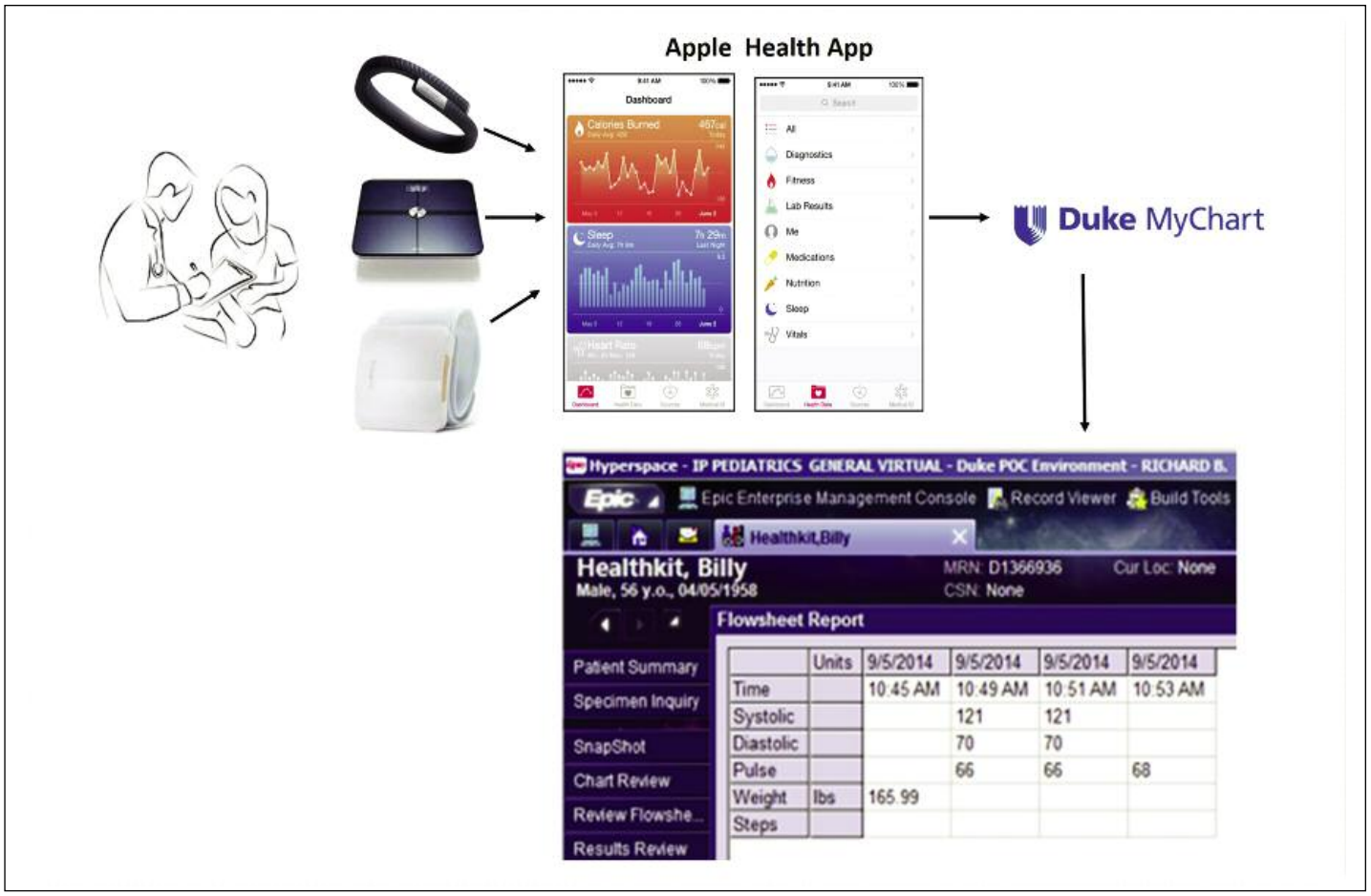

Figure 1. Patients enrolled in the study were given a wireless activity tracker, weight monitor, and blood pressure monitor. Data from these devices were transferred to the Health App on each patient's mobile phone. Through the Duke MyChart App (patient health portal), each patient was able to transfer data from his or her Health App automatically to the electronic medical record (bottom right, Epic Systems Co.).

ing VEGF targeted therapy for metastatic renal cell carcinoma.

Methods

Two patients starting oral VEGF receptor TKI therapy for mRCC consented to enroll in a pilot clinical research trial. Patients were provided a wireless blood pressure monitor (iHealth Feel, iHealth Labs Inc.), a wireless weight scale (Smart body analyzer, Withings Inc.) and a physical activity tracker (UP24, Jawbone Co.). Patients were advised to use these monitors on a daily basis for ninety days at the beginning of starting therapy. Patients were taught how to transmit health data from these monitors to the Health App (Apple Inc.) on his or her smart phone. At our academic institution, patients can use the Duke MyChart App (patient portal) to send health data stored from the Health App directly into the electronic medical record called Maestro Care (Epic Systems, Co.). This data flow is shown in **Figure 1**. English speaking patients with home wireless internet access and an Apple mobile smartphone with the Health App (Apple Inc.) already installed were eligible to participate. The objectives were to demonstrate feasibility of data collection for this novel method of remotely monitoring mHealth data and also to compare electronically obtained mHealth data to information collected at interval clinic visits.

Results

Case 1

An 81-year-old female with a past medical history notable for hypertension, was diagnosed with metastatic renal cell carcinoma with metastases to the right lower lobe of the lung with associated large pleural effusion. At diagnosis, she underwent a right radical cytoreductive nephrectomy with pathology showing grade IV clear cell renal cell carcinoma. The patient started pazopanib 800 mg daily post-nephrectomy, and developed worsening treatment-related hypertension in the subsequent weeks. Five weeks after initiating pazopanib, she awoke from sleep with acute onset of shortness of breath and presented to the emergency department where her ejection fraction was 35%, her cardiac enzymes were negative, and her B-type natriuretic peptide (BNP) was elevated. She was admitted to the hospital, and initiated on heart failure therapy for what was presumed to be pazopanib induced cardiomyopathy. With aggressive medical management including diuretics, and antihypertensive therapy, her ejection fraction normalized and she had a repeat echocardiogram

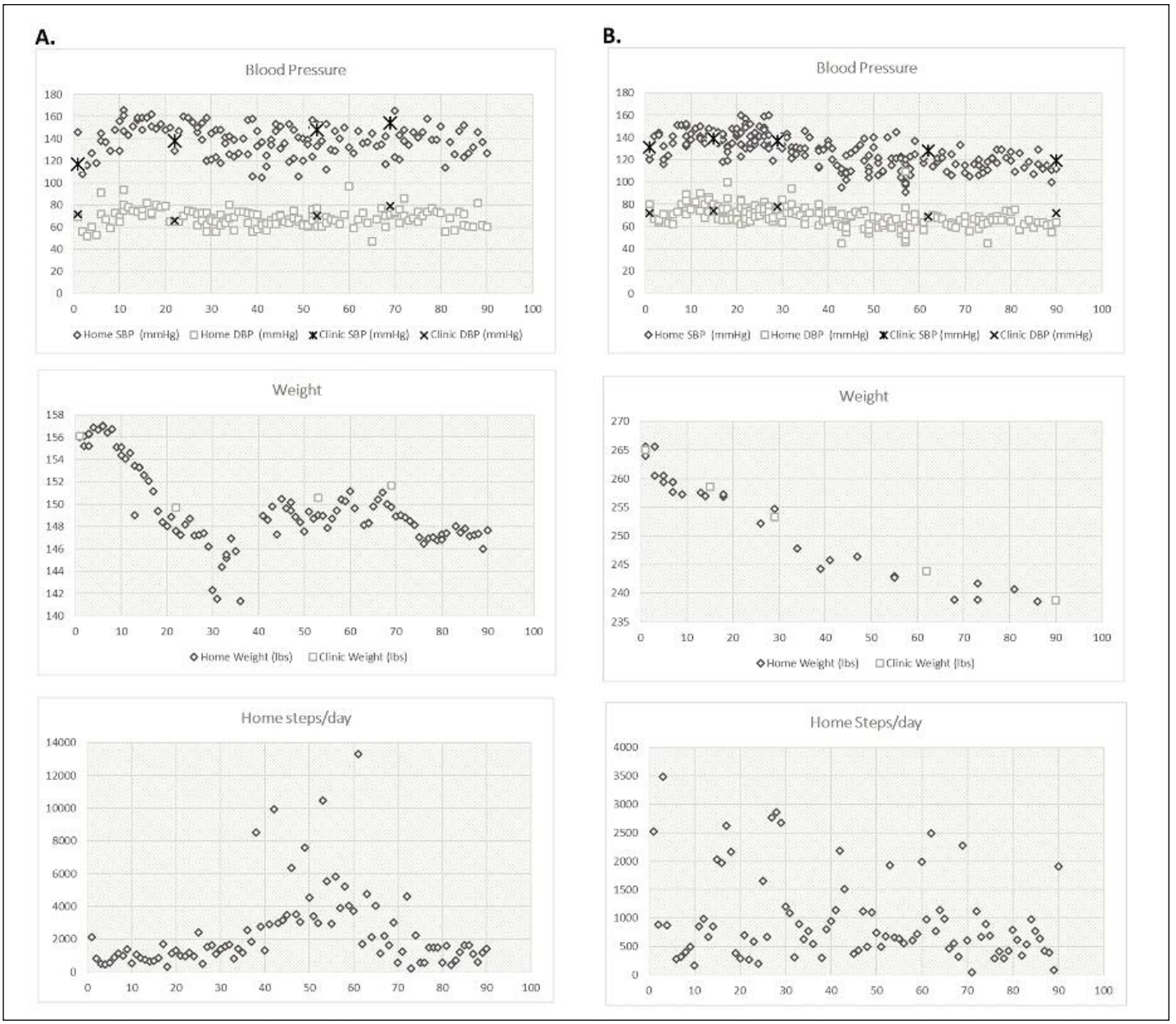

Figure 2. Blood pressure, weight, and steps/day changes for patient 1 (A) and patient 2 (B) for 90 consecutive days. X axis shows days on treatment. Home (remote monitoring) versus clinic readings are shown. For patient 1, axitinib was initiated on day 6. For patient 2, pazopanib was initiated on day 1. SBP = Systolic blood pressure. DBP = Diastolic blood pressure.

showing EF of 59%. The patient had a very nice response to pazopanib with a resolved pleural effusion and decreased size of her right lower lobe pleural effusion, but was switched to everolimus due to cardiotoxicity from pazopanib. The patient progressed on everolimus, and for third line systemic therapy, she was started on axitinib (another VEGF receptor-TKI) at a low dose of 3 mg twice daily. Of clinical concern was that the patient could be at high risk for repeat cardiotoxicity when starting axitinib therapy and needed close monitoring of her cardiovascular status including blood pressure.

Prior to starting on axitinib the patient was enrolled in our clinical study, and we initiated daily home blood pressure, weight, and activity monitoring with mHealth technology. To minimize her risk of cardiotoxicity, we aimed to keep her blood pressure less than 140/90. **Figure 2A** shows her blood pressure at four interval clinic visits during the first 90 days compared to the data from home blood pressure monitoring. In this particular case, home blood pressure monitoring detected blood pressure rises above SBP > 140 more quickly than monitoring only during clinic visits. Anti-hypertensive medications were uptitrated at the first interval clinic visit, which was approximately 2 weeks after the initiation of axitinib therapy. Significant weight loss was detected sooner with mHealth monitoring compared to interval clinic visits. Also of interest, her performance status was measured at KPS 90 and ECOG of 1 during each clinic visit during the 90-day

interval. Her steps/day are shown during this same time period. The patient had re-staging scans three months into treatment with axitinib, which had shown stable disease at the time.

Case 2

A 70-year-old gentleman with a history of hypertension, sleep apnea, diabetes, and obesity presented with painless gross hematuria. The patient's imaging at presentation showed a left lower pole renal mass, enlarged periaortic and retroperitoneal lymph nodes, and bilateral pulmonary nodules. The patient underwent a cytoreductive nephrectomy, and pathology was consistent with clear cell RCC. The patient also had an endo-bronchial metastasis blocking 90% of the right main-stem bronchus and partially obstructing the left main-stem bronchus requiring a laser tumor ablation. Subsequent to this ablation, he was started on pazopanib post operatively.

Prior to starting on pazopanib he was enrolled onto our clinical study. Mobile health technology was used to monitor the patient's blood pressure, physical activity, and weight changes after initiating treatment (**Figure 2B**). Due to this patient's cardiovascular co-mor- bidities, blood pressure monitoring was important. Blood pressure readings at home and during 5 interval clinic visits are shown. Weight changes are picked up earlier through home monitoring as shown. The patient's performance status was assessed as ECOG 1 during each clinic visit, KPS was not assessed. Steps per day are shown as well. Unfortunately, this patient had progressive disease after his first re-staging CT scan 3 months after initiating pazopanib therapy. Subsequently, he was taken off of pazopanib and started on everolimus, which was the standard second line therapy at the time.

"In an era where newer treatments for renal cancer including targeted agents, immunotherapies, and combination approaches continue to expand rapidly, we believe this feasibility study is an important first step in a continuum of research to eventually design larger interventional trials, which will validate and better define how mHealth can help improve clinical outcomes in this patient population."

Discussion

The concept of home health monitoring is not new as telehealth applications have been well established in the care of chronic diseases such as hypertension, diabetes and COPD.[6-9] However, as commercially available mHealth technology continues to become more sophisticated, medical professionals are slow to incorporate and validate the usefulness of new methods of home monitoring.[4,5] Providing an efficient, secure method to transmit mHealth data from patients to providers is necessary. One major limitation to the use of mHealth in clinical care is the lack of methods to incorporate mHealth data easily into our health information systems.[15] In this initial pilot study, we are able to demonstrate the feasibility of successfully transferring mHealth blood pressure, weight, and physical activity data by two patients electronically into the medical record easily available for review by the investigators. It should also be noted that both patients were fairly compliant with mHealth monitoring. No formal reminders were provided to patients to continue using their devices. The fact that the data from the devices flows directly into the electronic medical record is important to note as it allows a mechanism for health providers and nurses to monitor this data. Furthermore, the technology used in this study involves an electronic platform by Epic Systems Co., which is an electronic medical record system used widely, and as a result may have generalizability for larger scale use. Having an efficient mechanism for patients to share data is an essential first step to being able to validate and incorporate mHealth into clinical care.

We believe there is a role to expand the use of mHealth applications on a larger scale as well. Detecting, and intervening on real-time clinical changes based on mHealth monitoring may have potential to help improve treatment efficacy, prevent hospitalizations, prevent hospital resource utilization, and improve survival in patients with renal cell carcinoma. In the case studies presented, patients had metastatic renal cell carcinoma and were treated with VEGF receptor TKIs, a class of oral medications that have different dosing levels and a wide variety of common side effects.[1-3] Detection and management of these side effects quickly is essential, given that maintaining dose intensity of VEGF receptor TKIs improves patient survival.[13] Blood pressure increases are thought to be a direct on-target side effect of inhibiting the VEGF receptor. Recognizing and treating hypertension may be important to prevent morbidity such as heart failure, PRESS syndrome, and cardiovascular events in patients. For instance, in ***Case 1***, blood pressure increases were detected through mHealth monitoring even prior to the first interval clinic visit, which may have provided an earlier opportunity for clinical intervention in this case. Previous studies have shown that home BP monitoring in patients receiving VEGF receptor TKIs is important to detect as occult rises in blood pressure can be missed by measuring only at clinic visits.[16] Weight loss in patients with cancer is common, especially in patients being treated with medications that cause gastrointestinal side effects. In both cases presented, weight loss was more evident even during the first few weeks of therapy through home monitoring. This may serve as a way to detect potential gastrointestinal intolerability as well as design symptom management to combat weight loss sooner. It should be noted that with respect to home monitoring of weight and blood pressure, measurements between home and clinic monitoring were fairly similar from an accuracy standpoint (**Figure 2**); although some health monitoring devices such as the blood pressure cuff used in this study are FDA approved, many are not. While much still needs to be done in terms of validating the accuracy of particu-

lar health monitors, the precision and benefits of real time monitoring in the cases presented here appears to give valuable clinical information.

Both patients in this case study presented were shown to have a robust performance status of ECOG of 1. This generally indicates patients who are fairly active with normal activity and minimal symptoms. Both patients consistently took less than 5000 steps/day, which is often considered to be sedentary behavior.[17] Home monitoring of physical activity could provide a better assessment of performance status. Furthermore, being able to detect real time changes in activity patterns may provide a more objective manner to quantify changes especially when it comes to subjective clinical assessments such as fatigue, functionality, and quality of life.

Finally, it is worth mentioning that two recent studies in cancer patients also emphasize the importance of prompt symptom detection in patients with cancer. A phase III clinical trial (NCT02361099) in 121 patients with metastatic lung cancer showed how a web application based surveillance approach to capture symptoms improved patient survival compared to standard of care interval clinic based symptom monitoring (19 months vs. 11.8 months).[11] Just recently, another clinical trial (NCT00578006) showed how using a web-based symptom monitoring patient reported outcomes (PROs) tool, which automatically alerted health care providers to severe or worsening patient symptoms, improved survival compared to usual care in outpatient cancer patients receiving chemotherapy (31.2 vs 26.0 months).[18]

Conclusions

It is important to acknowledge that there are many hurdles to consider in regards to expanding mHealth applications in cancer care. These include the potential for breach of privacy of patient health information, validation of the accuracy of mHealth sensor technology, health care cost and reimbursement, as well as the issue of determining how to triage clinical responses to real time monitoring of health information. Our current report shows how mHealth can be used to remotely monitor clinical parameters such as blood pressure, weight, and physical activity, which are important for patients with mRCC treated with VEGF inhibitors. In an era where newer treatments for renal cancer including targeted agents, immunotherapies, and combination approaches continue to expand rapidly, we believe this feasibility study is an important first step in a continuum of research to eventually design larger interventional trials, which will validate and better define how mHealth can help improve clinical outcomes in this patient population.

Legend

BP - Blood pressure
FDA - Food and Drug Administration
mRCC - metastatic renal cell carcinoma
VEGF - vascular endothelial growth factor
TKI's - tyrosine kinase inhibitors
mTOR - mammalian target of rapamycin
App - Application
BNP - B-type natriuretic peptide

Conflict of Interest

Richard A. Bloomfield Jr was Director of Mobile Technology Strategy for Duke University Health System at the time this clinical trial was designed and completed. He currently works for Apple, Inc.

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A Dynamic Agenda Presented by the Society of Urologic Oncology

November 29 - December 1, 2017, Washington, DC

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The 18th annual meeting of the Society of Urologic Oncology presented an agenda covering a broad spectrum of topics in genitourinary cancers, including a significant amount of emerging data on renal cell carcinoma. These findings offer an intriguing picture of how the field is evolving in many directions, from prognostic factors, genomic analysis and biomarkers to surveillance protocols, surgical outcomes and emerging data on pathology. There is much more to discover in this report. The posters are worth reviewing to obtain a sense of where investigative work is likely to present results with potential impact on the standard of care, or, at the least, will point toward directions to be explored at future scientific sessions.

Basic and Translational Research

Xu et al (Poster #31) studied the role of sphingosine kinase 1 (SphK1) in cell lines and patient specimens (including plasma) at the RNA and protein level. In additional functional and preclinical therapeutics studies were performed. The authors identified SphK1 upregulation as a poor prognostic factors in patients with RCC. In addition, SphK1 overexpression could result in RCC progression thru the Akt/mTOR pathway, and is a potential regulator of HIF pathways. In addition, the use of a SphK1 inhibitor resulted in improvement of sunitinib efficacy in preclinical models.

Lokeshwar et al (Poster #32) performed miR profiling on 54 tumor samples and 59 controls. They noted that a combination of altered 3 miRs (miR-21, miR-142-5p, and miR194) was associated with worse survival outcomes. In addition, these markers were validated using 311 patients from the kidney cancer TCGA.

Wu et al (Poster #33) used a next-generation sequencing panel of 23 known and potential RCC predisposition genes to study germline mutations in 190 Chinese patients with RCC diagnosis under the age of 45 years. They noted that 9.5% of patients had germline mutations in 10 of the genes, including 12 patients with mutations in known RCC genes (BAP1, VHL, FH, PBRM1, TSC1/2, FLCN).

Ghanaat et al (Poster #156) studied 281 patients with non-metastatic RCC who underwent surgery, and had genomic analysis of VHL, PBRM1, SETD2, BAP1, and KDM5C done. 33 patients developed metastatic disease at median follow up of 9 years. This more recent cohort was used to validate the 2008 MSKCC nomogram to predict metastatic disease in patients who undergo definitive surgery. The authors noted that the nomogram is still valid and accurate in this more recent patient population, and that KDM5C mutation status was still significant when incorporated into this nomogram.

Sanchez et al (Poster #163) used flow cytometry to study tumor microenvironment (TME) in 48 patients who underwent renal surgery. The authors noted that total CD8+ T-cell population was not associated with poor oncologic features, however the rate of resident CD8+ T-cells (CD8a+CD49a+CD103-) was associated with advanced stage at diagnosis.

Bhindi et al (Poster #53) evaluated Bim expression in peritumoral lymphocytes in 525 patients with metastatic clear cell RCC who underwent radical nephrectomy (169 patients had synchronous metastases), and found that high Bim expression was associated with worse CSS and OS in this cohort.

Lane et al (Poster #159) conducted a pilot study of measuring urine biomarkers using an ELISA multiplex assay in patients undergoing surgery (20 partial, and 2 radical nephrectomy). They performed selective ureteral catheterization of the operated kidney and foley catheter drainage to measure the biomarkers selectively. The au-

thors noted that some biomarker levels are affected by blood contamination during resection, as well as induction of anesthesia per se. These results are important to account for confounders in future studies looking at the correlation of urinary biomarkers with surgical and renal functional parameters.

Pruthi et al (Poster #50) performed a radiogenomic study correlating image "roughness" as calculated from CT scans, with miR expression in 19 patients with clear cell, chromophobe and papillary RCC. They found that miR-10a, miR-10b, and miR-100 levels were inversely correlated with image roughness, while miR-21/miR-10b ratio was positively correlated with image roughness and could potentially differentiate RCC subtype.

Desai et al (Poster #157) studied the role of preoperative MRI in characterizing the tumor-parenchyma interface in 43 patients with a small renal mass who underwent robotic partial nephrectomy. All tumors had a visible pseudocapsule on MRI. 76.7% of the described pseudocapsules were circumferential, while 18.6% were fragmented and 4.7% were invasive. A pseudocapsule was identified in all tumor specimens on histologic evaluation. The authors noted that the presence of a fragmented or invasive pseudocapsule on preoperative MRI was associated with a higher i-Cap score.

Outcomes Research

Non-metastatic

Active surveillance

Petros et al (Poster #39) studied conditional survival a cohort of 272 patients enrolled in a prospective active surveillance protocol for small renal mass. They noted that patients who reached the 2-year landmark had an improved likelihood of survival to 5 years. Multivariable analysis revealed that eGFR, Charlson Comorbidity Index, and tumor size of 3-4 cm were predictive of overall survival at baseline and at the 2-year landmark. Interestingly, patients with tumor size of 3-4 cm were at a higher risk of non-RCC death.

Pruthi et al (Poster #49) reviewed the outcomes of active surveillance of 106 patients with 140 renal cystic lesions deemed to be Bosniak 2F or higher. Patients had a median follow up of 46 months, with a median of 7 abdominal scans performed. Bosniak 3 cysts were divided into 3s (enhancing septation) and 3n (nodularity present). The authors found that Bosniak 3s were more likely to regress, Bosniak 3n were more likely to progress, with no difference in growth rates between Bosniak 4 and non-Bosniak 4 cysts, and no development of metastatic disease in any of the patients on surveillance.

Pathology

Westerman et al (Poster #42) used a large RCC cohort to study 158 patients with cystic clear cell RCC. These patients were noted to be younger, have more cystic features on imaging, did not present with metastatic disease, and had no sarcomatoid dedifferentiation and only 1% rate of coagulative tumor necrosis, when compared with non-cystic RCC. Only 1 of the 158 patients with cystic RCC died of RCC (median follow up of survivors was 10.5 years), highlighting the favorable prognosis of this group of patients.

Bhindi et al (Poster #54) characterized a large cohort of patients with RCC treated with surgery into indolent versus aggressive, instead of the more commonly used terminology of benign versus malignant. Indolent tumors consisted of low-grade clear cell RCC, low-grade papillary RCC, low-grade translocation-associated RCC, any chromophobe, clear cell papillary, mucinous tubular and spindle cell, tubulocystic, and SDH-B deficient RCC. The authors noted that the 10-year CSS of patients with indolent malignant tumors was 96%, compared to 82% for those with aggressive tumors. In addition, they calculated the risk of malignancy and aggressiveness based on tumor size and sex. They noted that with increasing tumor size, the probability of malignancy reaches 90% at around 4cm, and plateaus afterwards, while the risk of aggressiveness continues to increase with larger tumor sizes. Not surprisingly, for any particular size, the risk of aggressive histology was higher in males than in females.

Hamilton et al (Poster #37) used a multi-institutional cohort of 2640 patients with non-metastatic RCC to analyze the nuances in staging pT3a patients. They noted that those patients who were considered cT1 and were upstaged at surgery to pT3a had similar outcomes to patients with pT2 disease, and those patients with cT2 upstaged to pT3a were more in line with cT3a upstaged to pT3a. The authors are suggesting a modification to the TNM staging system based on these data, after appropriate confirmatory studies are done.

Reddy et al (Poster #168) used a similar cohort of patients to compare outcomes of patients who underwent radical nephrectomy or partial nephrectomy, and were upstaged at surgery to pT3a, and noted that patients who underwent partial nephrectomy were at a higher risk of positive surgical margin, lower risk of blood transfusion, and lower risk of GFR<60. There were no differences in complication rates or oncologic outcomes when comparing upstaged pT3a patients who underwent radical nephrectomy versus partial nephrectomy.

Renal function

Isharwal et al (Poster #148) studied the impact of preoperative comorbidities on recovery of renal function after partial nephrectomy using 405 patients from a single institution. The authors showed that the primary determinant of renal functional recovery was parenchymal preservation, followed by ischemia characteristics (cold versus warm, duration), and was independent of comorbidities.

Klinger et al (Poster #158) used a cohort of 336 patients from an international collaboration to study the correlation of preoperative assessment of volume preservation (PAVP) and surgeon postoperative assessment of volume preservation (SAVP) with postoperative renal functional outcomes in patients undergoing partial nephrectomy. The authors noted that PAVP and SAVP were moderately correlated with each other, and that they were correlated with postoperative GFR.

Surgical outcomes

Ingham et al (Poster #153) studied the effect of aspirin on outcomes of over 10,000 patients undergoing partial nephrectomy using the Premier Hospital Database. 774 patients were noted to be taking aspirin. Patients on aspirin undergoing minimally invasive partial nephrectomy were less likely to need a blood transfusion. Patients on aspirin were more likely to experience a major cardiovascular event regardless of surgical approach.

Baiocco et al (Poster #161 and Poster #162) evaluated the role of multiplex partial nephrectomy MPN (partial nephrectomy for 3 or more tumors) in solitary kidneys, and compared outcomes with patients undergoing standard partial nephrectomy (SPN). The authors noted that patients who underwent MPN had more blood loss, more blood transfusions, longer hospital stay, higher rate of Clavien grade 3 complications, more need for permanent hemodialysis, and higher local recurrence rates. In addition, the outcomes were not statistically different in patients undergoing repeat MPN abd those patients undergoing initial MPN.

Ryan et al (Poster #169) studied the effect of diabetes mellitus on outcomes in 3,041 patients with RCC treated with surgery. The authors noted that diabetes did not impact recurrence free survival in RCC, but only overall survival. They also noted that patients with stage I RCC, those who had radical nephrectomy in the setting of being diabetic had worse outcomes compared to those who had partial nephrectomy and those without diabetes, while diabetes was not associated with overall survival in patients with stage II-IV.

Ristau et al (Poster #151) studied the safety and effectiveness of partial nephrectomy in a cohort of patients with high-complexity tumors (RENAL nephrometry score 10-12) treated at 4 institutions. They did not note a difference in 30-day complications between partial nephrectomy and radical nephrectomy. On multivariable analysis, recurrence-free survival was higher for patients who underwent partial nephrectomy, while overall survival was not different, indicating a likely selection bias.

Gomella et al (Poster #155) studied the outcomes of nephrectomy and lymphadenectomy in 17 patients with hereditary leiomyomatosis and RCC with clinically positive nodes. Median number of nodes removed was 24, and median number of positive nodes was 4. Four patients (24%) were still disease free at time of last follow-up, while 9 patients (69%) had tumor recurrence within the lymphadenectomy template boundaries, pointing toward the need for more aggressive systemic therapy in this patient population.

Other

Kaushik et al (Poster #142) used an open-source platform to study kidney cancer care disparities in South Texas (within the catchment area for University of Texas Health Science Center in San Antonio). The authors noted that kidney cancer incidence was significantly higher in Hispanics compared to Non-Hispanic Whites, in all ages groups over 20, with a strong male to female ratio.

Xia et al (Poster #43) used the NCDB to investigate the correlation between hospital volumes and outcomes of over 18,000 patients who underwent robotic assisted partial nephrectomy, and found that higher volume hospitals experience better outcomes (lower rate of conversion to open surgery, lower rate of hospital stay>3 days, and lower rate of positive surgical margins).

Metastatic

Peyton et al (Poster #38) used a cohort of 293 patients with metastatic RCC with IVC tumor thrombus to study the prognostic role of neutrophil-lymphocyte ratio (NLR). Patients with lower NLR experienced longer overall survival. They noted that NLR could substratify patients with intermediate risk MSKCC (but not good or poor risk patients) into 2 clearly different groups (OS of 24 months versus 12 months for those with low NLR versus high NLR, respectively).

Martin et al (Poster #146) used a cohort of patients with metastatic RCC with primary in place, enrolled on a phase 3 clinical trial of sunitinib versus sunitinib + AGS-003, to study chronic kidney disease after cytoreductive nephrectomy in patients with preoperative GFR over 60. Of the 371 patients, 45.5% developed stage 3 or worse chronic kidney disease on short-term follow-up. Factors that predicted this finding included age, hypertension, Charleson Comorbidity Index, history of renal stones, and presence of liver metastatic disease.

Xia et al (Poster #41) used the NCDB to evaluate patients with RCC with oligometastatic disease from 2010-2013 who underwent cytoreductive nephrectomy, in order to study the value of metastasectomy in this cohort. Of the 2395 patients in this study, 14.7% underwent a metastasectomy. Patients who underwent a metastasectomy were noted (while controlling for comorbidity) to have longer OS (HR=0.65, OS of 37.5 months versus 20.8 months in no-metastasectomy patients), and to receive targeted therapy less frequently (44.0% versus 56.1%).

Woldu et al (Poster #52) used the NCDB to study the effect of delay of receiving targeted therapy on outcomes of 2716 patients with metastatic clear cell RCC. They noted that a delay in receiving targeted therapy (divided in subgroups of less than 2 month, 2-3 months, 3-6 months, and over 6 months) was not associated with worse outcomes in this patient population, keeping in mind that selection bias was an important factor in this delay.

Xia et al (Poster #145) used the NCDB to study short-term outcomes after cytoreductive nephrectomy in relation to hospital volume. Hospitals with 8 or more cases per year were considered high-volume for the purpose of this study. Patients treated at high-volume hospitals experienced lower rates of 30-day and 90-day mortality, prolonged length of stay, and 30-day readmission. In addition, these outcomes were noted to improve more with higher numbers of surgeries performed within these centers.

Lenis et al (Poster #147) used the NCDB to study trends and effects of overall survival of surgery in patients with metastatic RCC and IVC tumor thrombus. The authors noted that patients with T3b and T3c potentiallywere less likely to undergo surgery than those with T3a disease. In this cohort, cytoreductive nephrectomy was associated with improved survival in patients with T3a and T3b, but not T3c disease. KCJ

EDITOR'S MEMO

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to an IRC analysis, this phase is likely to reveal a tendency in the earlier stages of the trial to be somewhat sanguine about outcomes. For example, among RCC patients who have shown, let's say, a 25% reduction in tumor size, investigators may characterize this finding as a "partial response." However, such responses scrutinized in the IRC analysis may be recategorized because the review suggests otherwise. This is particularly true when evaluations of whether end points have been reached are considered in a relatively subjective context.

The advantage of having an independent review board review all the radiological data was important. With regard to this IRC data, the reviewers are not aware of which patients are assigned to a drug. And they are not aware of what the investigators had said about these patients. The board simply measures the tumors and whether there was progression or reduction. The bottom line is that a major question mark regarding the validity of results previously presented through the CABOSUN trial has essentially been lifted. The robust data translate to an improvement in outcomes for patients in first line therapy who are intermediate to poor risk compared to treatment with sunitinib.

Results presented at ESMO with respect to CABOSUN were important for other reasons as well, particularly as we look for evidence on progression-free survival (PFS) and overall survival OS) to guide clinical decision making. CABOSUN did not produce definitive data on OS because the trial was not large enough for that measure. Nevertheless, CABOSUN did show an overall survival benefit trend. But with all the combinations emerging and undergoing study (such as a new trial investigating ipi-nivo combined with cabozantinib) we need to question the wisdom of spending years on assessing this end point with monotherapy, whether it achieves improved OS. Practically speaking, it may be superfluous and not a good investment for a pharmaceutical company's research program to undertake this study. Why? Because it is likely that a combination of agents, including the drug for which OS has not been unequivocally determined, will produce data showing superior OS.

As we evaluate the expanded spectrum of therapy and the overarching excitement for immune-oncologic approaches, the subtext of the debate is also a cautionary tale. As impressive as the OS findings are with IO therapy, not all patients are candidates for IO. The cautionary tale reflects the fact that in many patients IO therapy may not be the appropriate first choice—particularly in those with bone metastases, autoimmune disease and the elderly whose ability to undergo infusions may be limited.

With this issue, we conclude our 15th year of publishing the *Kidney Cancer Journal*. Who would have known that when this publication was launched in 2003 that we would be talking about "future shock" and an overwhelming volume of information in frontline therapy? At that time there was only one drug approved for RCC Perhaps the new year will bring much in the way of a new paradigm, as much perhaps as what the situation was more than 10 years ago when the current standard of anti-VEGF therapy was about to be approved. On behalf of the journal, its Medical Advisory Board and Editorial Advisory Board, we wish you the best for the new year.

Robert A. Figlin, MD
Editor-in-Chief

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MVD correlated with Fuhrman grade 1-2 ($P < 0.001$), clear cell histology ($P < 0.001$), and absence of necrosis ($P < 0.001$) but not with gender, age, sarcomatoid features, lymphovascular invasion, or tumor size.
Conclusion: High MVD in resected high-risk RCC patients is an independent prognostic, rather than predictive, biomarker of improved OS. Further studies should assess whether incorporating MVD into clinical models will enhance our ability to predict outcome and if low MVD can be used for selection of high-risk patients for adjuvant therapy trials.

Multicenter Validation of Enhancer of Zeste Homolog 2 Expression as an Independent Prognostic Marker in Localized Clear Cell Renal Cell Carcinoma. Ho TH, Kapur P, Eckel-Passow JE, et al. *J Clin Oncol*. 2017 Nov 10; 35(32):3706-3713. doi: 10.1200/JCO.2017.73.3238.
Summary: Enhancer of zeste homolog 2 (EZH2), a chromatin remodeler, is implicated in the pathogenesis of clear cell renal cell carcinoma (ccRCC). However, the effect of EZH2 on outcomes in localized ccRCC is unclear, and molecular biomarkers are not currently integrated into prognostic models or adjuvant therapy trials. Methods We performed Cox regression to evaluate the association of tumor-based EZH2 gene and protein expression with survival in three independent cohorts: a cohort from The Cancer Genome Atlas (n = 532), a cohort from University of Texas Southwestern Medical Center (n = 122), and a cohort from Mayo Clinic (n = 1,338). Analyses were adjusted for the prognostic stage, size, grade, and necrosis (SSIGN) score as well as within low-, intermediate-, and high-risk SSIGN groups. Results Patients in The Cancer Genome Atlas cohort with EZH2-high gene expression were 1.5 times more likely to experience overall death than patients with EZH2-low expression (95% CI, 1.1 to 2.3; $P = .028$). Patients in the University of Texas Southwestern Medical Center cohort with EZH2-high protein expression were two times more likely to experience overall death than patients with EZH2-low expression (95% CI, 1.1 to 4.4; $P = .034$). Similarly, patients in the Mayo Clinic cohort with EZH2-high protein expression were 1.4 times more likely to experience overall death (95% CI, 1.2 to 1.7; $P < .001$). Patients in the Mayo Clinic cohort with EZH2-high protein expression were nearly two times more likely to experience RCC-specific death (95% CI, 1.5 to 2.6; $P < .001$); EZH2 protein expression was particularly prognostic among patients with low-risk SSIGN tumors (HR, 6.1; 95% CI, 3.4 to 11.1; $P < .001$).
Conclusion: EZH2 expression accurately predicts risk of RCC death beyond existing clinicopathologic models, particularly in low- and intermediate-risk SSIGN tumors. Further studies are required to incorporate molecular biomarkers into surveillance guidelines and adjuvant clinical trials.

Adjuvant Sunitinib for High-risk Renal Cell Carcinoma After Nephrectomy: Subgroup Analyses and Updated Overall Survival Results. Motzer RJ, Ravaud A, Patard JJ, et al. *Eur Urol*. 2017 Sep 26. Pii: S0302-2838(17)30772-8. Doi: 10.1016/j.eururo.2017.09.008.
Summary: Adjuvant sunitinib significantly improved disease-free survival (DFS) versus placebo in patients with locoregional renal cell carcinoma (RCC) at high risk of recurrence after nephrectomy (hazard ratio [HR] 0.76, 95% confidence interval [CI] 0.59-0.98; P=0.03). To report the relationship between baseline factors and DFS, pattern of recurrence, and updated overall survival (OS). Data for 615 patients randomized to sunitinib (n=309) or placebo (n=306) in the S-TRAC trial. Subgroup DFS analyses by baseline risk factors were conducted using a Cox proportional hazards model. Baseline risk factors included: modified University of California Los Angeles integrated staging system criteria, age, gender, Eastern Cooperative Oncology Group performance status (ECOG PS), weight, neutrophil-to-lymphocyte ratio (NLR), and Fuhrman grade. Of 615 patients, 97 and 122 in the sunitinib and placebo arms developed metastatic disease, with the most common sites of distant recurrence being lung (40 and 49), lymph node (21 and 26), and liver (11 and 14), respectively. A benefit of adjuvant sunitinib over placebo was observed across subgroups, including: higher risk (T3, no or undetermined nodal involvement, Fuhrman grade ≥2, ECOG PS ≥1, T4 and/or nodal involvement; hazard ratio [HR] 0.74, 95% confidence interval [CI] 0.55-0.99; P=0.04), NLR ≤3 (HR 0.72, 95% CI 0.54-0.95; P=0.02), and Fuhrman grade 3/4 (HR 0.73, 95% CI 0.55-0.98; P=0.04). All subgroup analyses were exploratory, and no adjustments for multiplicity were made. Median OS was not reached in either arm (HR 0.92, 95% CI 0.66-1.28; P=0.6); 67 and 74 patients died in the sunitinib and placebo arms, respectively.
Conclusion: A benefit of adjuvant sunitinib over placebo was observed across subgroups. The results are consistent with the primary analysis, which showed a benefit for adjuvant sunitinib in patients at high risk of recurrent RCC after nephrectomy. Most subgroups of patients at high risk of recurrent renal cell carcinoma after nephrectomy experienced a clinical benefit with adjuvant sunitinib. KCJ

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sunitinib versus 51.3% for placebo. Median overall survival findings were not yet mature at the time of the analysis; however, the hazard ratio between the two arms for survival was 1.01 (95% CI, 0.72-1.44; *P* = .94).

The investigator assessed median DFS in the sunitinib arm was 6.5 years compared with 4.5 years with placebo (HR, 0.81; 95% CI, 0.64-1.02; *P* = .08). In higher risk patients, the median DFS by investigator assessment was 5.9 versus 3.9 years for sunitinib and placebo, respectively (HR, 0.76; 95% CI, 0.58-1.01; *P* = .06).

Tivozanib Approved in Europe for Kidney Cancer

The European Commission (EC) has approved tivozanib (Fotivda) for the treatment of patients with advanced renal cell carcinoma (RCC). The drug is specifically approved for the frontline treatment of adult patients with advanced RCC and for adults with advanced RCC who are VEGFR- and mTOR-inhibitor mTOR-inhibitor naïve following disease progression after 1 prior treatment with cytokine therapy.

The approval, which follows a positive recommendation from the European Medicines Agency's Committee for Medicinal Products for Human Use, is based on the phase III TiVO-1 trial, in which tivozanib reduced the risk of disease progression or death by over 20% vs sorafenib (Nexavar) in patients with advanced RCC who received up to 1 prior line of therapy (excluding targeted agents). Patients assigned to tivozanib were more likely remain on full treatment dose (86% vs 57%; *P* = .001). Only 14% of patients in the experimental arm required dose reduction due to adverse events (AEs) compared with 43% in the sorafenib arm. Patients in the tivozanib group were also less likely to experience AEs usually associated with other VEGFR-TKIs including diarrhea (23% vs 33%) and hand-foot syndrome (14% vs 54%).

Researchers at Institut Gustave Roussy are currently evaluating tivozanib in combination with nivolumab (Opdivo) for patients with advanced RCC in the phase I/II dose escalation/expansion TiNivo trial. Additionally, results are anticipated in 2018 for the pivotal TIVO-3 trial, a randomized, controlled, multicenter, open-label study comparing tivozanib to sorafenib in patients with refractory advanced RCC.

TIVO-3 Study Futility Analysis Completed—No Changes to Protocol

AVEO Oncology has announced the completion of a pre-planned futility analysis of the Phase 3 TIVO-3 trial, the company's randomized, controlled, multi-center, open-label study to compare Fotivda® (tivozanib) to sorafenib in subjects with refractory advanced renal cell carcinoma (RCC). Based on results of the futility analysis, which was reviewed by an independent statistician, the study will continue as planned without modification. This analysis did not allow for early stopping due to efficacy to assure adequate follow-up for the key secondary endpoint of overall survival. The pre-planned futility analysis was triggered by the reporting of 128 progression events in early August. Additional events were recorded as part of the data management process leading into the futility analysis, resulting in a revised data cut-off date for the analysis of May 29. The Company continues to expect the TIVO-3 to read out in the first quarter of 2018.

The TIVO-3 trial, together with the previously completed TIVO-1 trial of tivozanib in the first line treatment of RCC, is designed to support regulatory approval of tivozanib in the US as a first and third line treatment for RCC. The TIVO-3 trial was designed to enroll patients with recurrent RCC who have failed at least two prior regimens, including VEGFR-TKI therapy (other than sorafenib). Eligible patients may also have received checkpoint inhibitor therapy in earlier lines of treatment. Patients are randomized 1:1 to receive either tivozanib or sorafenib, with no crossover between arms. The primary endpoint of the study is progression free survival. Secondary endpoints include overall survival, overall response rate, and safety and tolerability.

The TiNivo trial is a Phase 1/2 study of tivozanib in combination with Bristol-Myers Squibb's OPDIVO® (nivolumab), an immune checkpoint, or PD-1, inhibitor, for the treatment of RCC. The TiNivo trial is being led by the Institut Gustave Roussy in Paris under the direction of Bernard Escudier, MD, Chairman of the Genitourinary Oncology Committee. The trial advanced into the Phase 2 expansion portion following successful completion of the Phase 1 dose escalation portion. The combination was well tolerated to the full dose and schedule of single agent tivozanib, with no dose limiting toxicities. The expansion portion of the trial is expected to enroll an additional 20 subjects. Phase 1 results from the ongoing study have been submitted for presentation at a scientific meeting taking place in the fourth quarter.

Phase III IMmotion151 Study Shows Tecentriq (Atezolizumab) and Avastin (Bevacizumab) Reduced Risk of Disease Worsening or Death for Initial Treatment of Advanced RCC

TECENTRIQ and Avastin showed improvement in investigator-assessed progression-free survival (PFS) compared with sunitinib for patients whose disease expressed PD-L1. Data will be discussed with health authorities globally, including the FDA and European Medicines Agency.

Genentech has announced that the Phase III IMmotion151 study met its co-primary endpoint of investigator-assessed progression-free survival (PFS) and demonstrated that the combination of TECENTRIQ® (atezolizumab) and Avastin ® (bevacizumab) provided a statistically significant and clinically meaningful reduction in the risk of disease worsening or death (PFS). The results were in patients whose disease expressed the PD-L1 (programmed death-ligand 1; PD-L1 expression ≥1 percent) protein compared with sunitinib for first-line treatment of metastatic renal cell carcinoma (mRCC). KCJ

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