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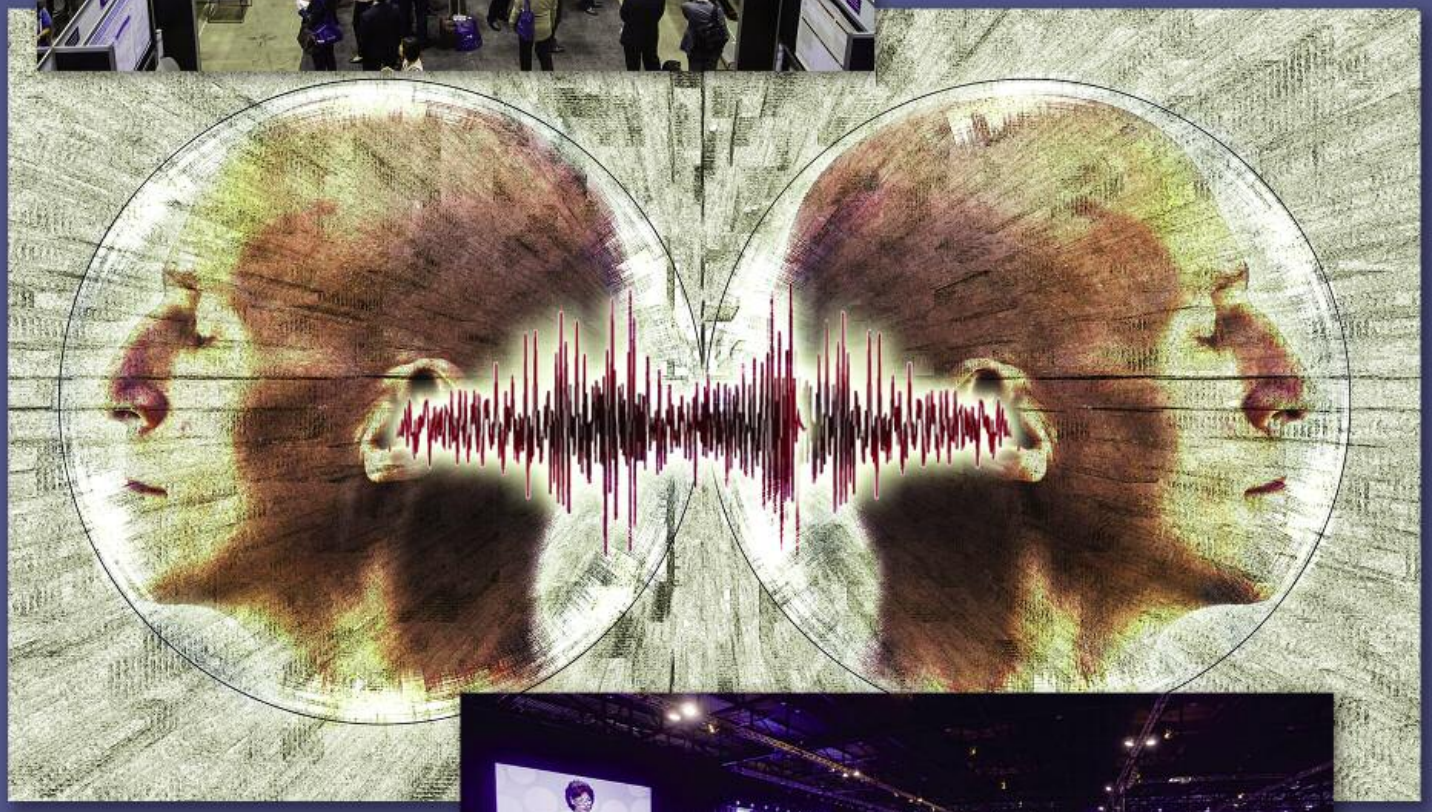
Meta-analysis Revisits Role of Sorafenib, Challenging Old Views

2017 GU ASCO Charts Intriguing Road Map of Future Directions



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

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.

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Inlyta®
axitinib 1mg and 5mg tablets

Continue the fight with INLYTA

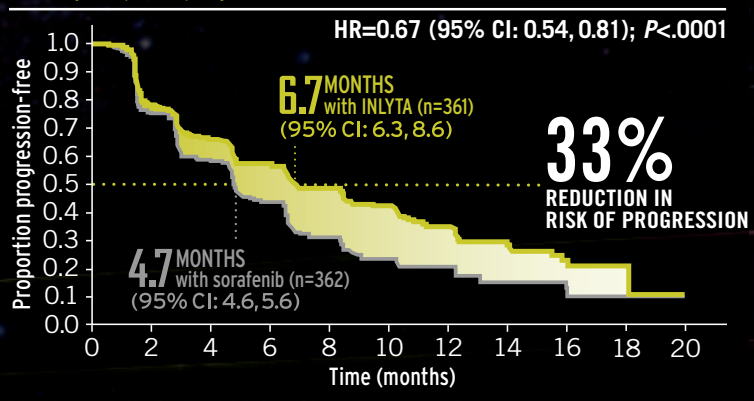
Proven efficacy with a distinct safety profile

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.

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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
Enhanced communication. That is the theme of this artist's rendering of how scientific symposia promote an exchange of ideas. The crowded sessions of the ASCO annual meeting are depicted in this composite image. Copyright © 2017 Photo Researchers, Inc. Credit: George Mattei / Science Source. All Rights Reserved.

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KCJ GUEST EDITOR'S MEMO

Medical Meetings 2.0: Do Symposia "Move the Needle" in Kidney Cancer? If Yes, How Much?


James Brugarolas, MD, PhD

How does one measure the impact of a medical meeting, particularly the ASCO scientific symposia that occur throughout the year and in June the huge international extravaganza attracting more than 30,000 attendees? There are no solid metrics to quantify the effect of a meeting. Yes, CME post-tests seek to measure the value of meetings but it is all based on the subjective responses of attendees filling out those forms for CME credit. And there are Keypad sessions where attendees rate how discussions may alter their practice patterns, but their actual impact is unclear.

Nevertheless, there are many "take home" messages from these symposia and for many attendees, these "messages" could have a lasting effect on kidney cancer care. Studies suggest changes in practice patterns tend to occur in a number of ways, one being the influence of peers through various clinical settings, consensus guidelines, Grand Rounds, and the medical literature. More recently, the introduction of care pathways forces change and limits physician autonomy, but that is a topic for a different day. Symposia, including those sponsored by ASCO, are playing a role as an intervening variable in the equation.

Nevertheless, it is intriguing also to consider a "subjective metric"— how scientific symposia can jolt our perceptions, debunk prevailing myths, and produce counterintuitive findings. A case in point: the 2017 GU ASCO sessions in Orlando in February. From more than 100 abstracts in renal cell carcinoma, we compiled some salient examples of how perceptions can at least begin to change as evolving data emerge on a broad spectrum of topics and controversies. A quick Q&A offers some challenging questions:

True or false: Among patients who discontinue immune checkpoint inhibitor therapy because of immune-related adverse effects, benefits are likely to continue even after treatment is stopped.

Some responding patients—44% in a small series—still had a durable response and remained off of any additional therapy for a median time of 20 months. Thus, the answer calls into question the need for continuous treatment with immunotherapy in all patients.

True or false: Obese patients with RCC experience longer survival than non-obese patients.

Although obesity increases the risk of RCC, obese patients may experience longer survival than non-obese counterparts as reported by the IMDC

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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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Contact information

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

Peer Review and Editing

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

Conflict of Interest

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

Manuscript Preparation

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

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

References

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

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Essential Peer-Reviewed Reading in Kidney Cancer

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

CheckMate 025 Randomized Phase 3 Study: Outcomes by Key Baseline Factors and Prior Therapy for Nivolumab Versus Everolimus in Advanced Renal Cell Carcinoma. Escudier B, Sharma P, McDermott DF, et al. *Eur Urol*. 2017 Mar 2; pii: S0302-2838(17)30099-4. doi: 10.1016/j.eururo.2017.02.010.

Summary: The randomized, phase 3 CheckMate 025 study of nivolumab (n=410) versus everolimus (n=411) in previously treated adults (75% male; 88% white) with advanced renal cell carcinoma (aRCC) demonstrated significantly improved overall survival (OS) and objective response rate (ORR). The minimum follow-up was 14 mo. Baseline subgroup distributions were balanced between nivolumab and everolimus arms. Nivolumab demonstrated an OS improvement versus everolimus across subgroups, including Memorial Sloan Kettering Cancer Center (MSKCC) and international Metastatic Renal Cell Carcinoma Database Consortium risk groups; age <65 and ³65 yr; one and two or more sites of metastases; bone, liver, and lung metastases; number of prior therapies; duration of prior therapy; and prior sunitinib, pazopanib, or interleukin-2 therapy. The benefit with nivolumab versus everolimus was noteworthy for patients with poor MSKCC risk. The mortality rate at 12 moths for all subgroups was lower with nivolumab compared with everolimus. ORR also favored nivolumab. The incidence of grade 3 or 4 treatment-related adverse events across subgroups was lower with nivolumab.

Conclusion: The trend for OS and ORR benefit with nivolumab for multiple subgroups, without notable safety concerns, may help to guide treatment decisions, and further supports nivolumab as the standard of care in previously treated patients with aRCC.

Discontinuing VEGF-targeted Therapy for Progression Versus Toxicity Affects Outcomes of Second-line Therapies in Metastatic Renal Cell Carcinoma. De Velasco, G, Xie W, Donskov F, et al. *Clin Genitourin Cancer*. 2017 Jan 12. pii: S1558-7673(17)30005-8. doi:10.1016/j.clgc.2017.01.005.

Summary: A significant subgroup of metastatic renal cell carcinoma (mRCC) patients discontinue vascular endothelial growth factor-targeted therapies (VEGF-TT) because of toxicity. Whether clinical outcomes differ in patients who receive second-line (2L) targeted therapy on the basis of reason for discontinuation of first-line (1L) therapy is unknown. In total, 1124 patients were identified: 866 patients (77%) discontinued 1L VEGF-TT because of disease progression, and 208 patients (19%) because of toxicity. The reason for discontinuation of 1L therapy did not differ according to IMDC risk group. Compared with patients who stopped 1L VEGF-TT because of disease progression, patients who stopped because of toxicity had greater clinical benefit (nonprogressive disease as best response) in 2L treatment (68% vs. 56%; $P = .023$) and longer OS (17.4 vs. 11.2 months; $P = .0002$) adjusted for type of therapy, time to initiation of 2L treatment, IMDC risk group, and number of metastases at initiation of 2L treatment.

Conclusion: mRCC patients who discontinue 1L VEGF-TT because of toxicity have better outcomes with 2L therapy than patients who stop therapy because of disease progression. These findings should be taken into consideration when designing clinical trials for 2L therapies in mRCC.

Adjuvant Treatment for High-Risk Clear Cell Renal Cancer: Updated Results of a High-Risk Subset of the ASSURE Randomized Trial. Haas NB, Manola J, Dutcher JP, et al. *JAMA Oncol*. 2017 Mar 9. doi:10.1001/jamaoncol. 2017.0076.

Summary: Given recently published results of a 750-patient adjuvant sunitinib trial showing improved disease-free survival (DFS), the appropriate strategy for treating high-risk patients is unclear. This studydetermined whether there is improved disease-free survival benefit to taking the active drug in patients with high-risk (pT3, pT4, node-positive) clear cell renal cancer (ccRCC) in the ASSURE trial (adjuvant sunitinib or sorafenib vs placebo in resected unfavorable renal cell carcinoma [RCC]), the largest adjuvant trial published to date.

To evaluate DFS and overall survival (OS) in ccRCC high-risk patients wererandomized to sunitinib or sorafenib vs placebo. Patients received 1 year of adjuvant sunitinib (50 mg), sorafenib (800 mg) daily, or equivalent placebo. The study was amended for patient intolerance to sunitinib (37.5 mg), sorafenib (400 mg) daily, or equivalent placebo with mandatory dose escalation if no serious adverse effects were experienced. Of 1069 patients, 358 (243 [67.9%] men, 115 [32.1%] women) received sunitinib, 355 (248 [69.9%] men, 107 [30.1%] women) received sorafenib, and 356 (254 [71.3%] men, 102 [28.7%] women) received placebo as adjuvant therapy. Five-year DFS rates were 47.7%, 49.9%, and 50.0%, respectively for sunitinib, sorafenib, and placebo with 5-year OS of 75.2%, 80.2%, and 76.5% There was no difference by dose quartile.

Conclusion: Neither prognostic category of the tumor nor dose intensity of therapy altered the lack of difference in DFS or OS in this population of patients with high-risk ccRCC.

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

Cabozantinib Recommended as Option for Previously Treated Advanced RCC Regardless of Prior Systemic Therapy

AMSTERDAM, THE NETHERLANDS—A study of clinical outcomes according to prior therapies in the phase 3 METEOR trial of cabozantinib vs everolimus in advanced renal cell carcinoma (RCC) has demonstrated that cabozantinib should be considered a treatment option for previously treated patients regardless of prior systemic therapy.

This finding was reported at the 2017 European Cancer Congress, from January 27 -30.

Toni Choueiri, MD, of Dana-Farber Cancer Institute, Boston, explained that determining the optimal sequence of systemic therapy in patients with advanced renal cell carcinoma remains a clinical challenge. METEOR evaluated cabozantinib, a tyrosine kinase inhibitor, vs everolimus in patients with advanced renal cell carcinoma who had been treated with at least one vascular endothelial factor receptor tyrosine kinase inhibitor (VEGFR TKI). Overall survival was significantly prolonged with cabozantinib vs everolimus (median 21 vs 16.5 months [hazard ratio 0.66, 95% confidence interval 0.53 – 0.83, P = .0003]). Progression-free survival and objective response rate were also significantly improved with cabozantinib vs everolimus. In METEOR, 658 patients were randomized 1:1 to cabozantinib (60 mg qd) or everolimus (10 mg qd), with stratification by Memorial Sloan Kettering Cancer Center risk groups and the number of prior VEGFR TKIs. Clinical outcome measures included progression-free survival (primary endpoint), objective response rate, overall survival, and safety.

The hazard ratio for overall survival for patients who had been treated with only one prior TKI was 0.65 (95% confidence interval 0.50 – 0.85) vs 0 (95% confidence interval 0.48 – 1.10) for patients who had received at least two prior TKIs.

Median overall survival was 21.4 months with cabozantinib vs 16.5 months with everolimus (hazard ratio 0.66, 95% confidence interval 0.47 – 0.93) in patients who had taken sunitinib as their only prior VEGFR TKI and 22.0 vs 17.5 months with everolimus (hazard ratio 0.66, 95% confidence interval 0.42 – 1.04) in patients who had received pazopanib as their only prior VEGFR TKI.

Dr Choueiri concluded that progression-free and overall survival, as well as the objective response rate were consistently improved with cabozantinib vs everolimus in subgroups based on prior systemic therapy of sunitinib or pazopanib as prior VEGFR TKI therapy and prior anti-PD1/PD-L1 therapy. He added that cabozantinib should be considered a treatment option for previously treated patients with advanced renal cell carcinoma regardless of prior systemic therapy.

Tivozanib Revisited: New Trials Seek to Improve on Earlier Results

CAMBRIDGE, MA—AVEO Oncology announced that its pivotal, Phase 3 TIVO3 trial, a randomized, controlled, multicenter, openlabel study to compare tivozanib to sorafenib in refractory advanced renal cell carcinoma (RCC), has successfully completed the first safety review by the study's Safety Monitoring Committee (SMC). The SMC concluded that no safety concern was observed for tivozanib and recommended that the study replace the small number of patients who dropped out prior to starting treatment.

The TIVO3 trial is enrolling substantially ahead of schedule, with topline data expected in the first quarter of 2018. The TIVO3 trial, together with the previously completed TIVO1 trial of tivozanib in the first line treatment of RCC, is designed to support regulatory approval of tivozanib in the US as first and third line treatment for RCC.

Tivozanib has high selectivity for VEGF and is designed to reduce off target toxicity, thereby increasing tolerability. Earlier results with tivozanib encountered problems with FDA approval.

In a related development, AVEO Oncology also announced that the first patient has been dosed in the Phase 1/2 AVEO-sponsored TiNivo trial evaluating tivozanib in combination with Bristol-Myers Squibb's anti-PD-1 therapy, Opdivo® (nivolumab), in advanced RCC. The study, which will be led by the Institut Gustave Roussy in Paris, is under the direction of Bernard Escudier, MD, Chairman of the Genitourinary Oncology Committee. The Phase 1 trial will evaluate the safety of tivozanib in combination with nivolumab at escalating doses of tivozanib and, assuming favorable results, is expected to be followed by an expansion Phase 2 cohort at the established combination dose.

"There is compelling scientific rationale for combining the antiangiogenic activity of VEGF inhibition with the immunologic activity of PD-1 inhibitors. Yet, to date, the tolerability of these combinations have been a challenge with currently approved VEGF TKIs and PD-1s," said Dr Escudier. "Tivozanib has been demonstrated to be the most selective VEGF inhibitor, delivering a uniquely favorable tolerability profile in past single agent and combination studies, and has the potential for minimal overlapping toxicities with immunotherapies. I look forward to understanding the clinical potential of combining tivozanib and nivolumab in the TiNivo study, and to the prospect of further improving outcomes in this very dynamic treatment area."

"VEGF-PD-1 combinations have yielded promising tumor response outcomes in renal cell cancer, yet the data presented to date point to challenging or prohibitive toxicity," said Michael Bailey, president and chief executive

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Role of Sorafenib in the Current Treatment Landscape for Previously Treated Advanced Renal Cell Carcinoma: A Systematic Review and Network Meta-analysis of Efficacy and Safety








From left: Nicholas Vogelzang, MD, FASCO, FACP[1]; Thomas Hutson, DO, PharmD, FACP[3]; Marissa Blieden, MS: Corresponding Author[4]; Kyle Fahrbach, PhD[5]; Rachel Huelin, BA[6]; Adriana Valderrama, PhD, MBA[7]; Lonnie Wen, RPh, PhD[8]; Svetlana Babajanyan, MS, MD[9]
Not pictured: Thomas Powles, MBBS, MRCP, MD[2]

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Introduction

Previously, the standard of care for advanced/metastatic renal cell carcinoma (RCC) consisted primarily of interleukin-2 (IL-2) or interferon-alfa (IFN-α).[1] Since 2005, new targeted therapies have proven superior to cytokines for the first- and second-line treatment of RCC, including sorafenib, sunitinib, bevacizumab (in combination with IFN-α), pazopanib, temsirolimus, everolimus, and axitinib.[2] Additionally, since November of 2015, the United States (US) Food and Drug Administration (FDA) has approved three new treatments for RCC: nivolumab (a programmed death 1 [PD-1] inhibitor),[3,4] lenvatinib (a tyrosine kinase inhibitor [TKI], as either monotherapy and in combination with everolimus),[5,6] and cabozantinib (another TKI).[7,8]

According to the European Society for Medical Oncology (ESMO) 2014 guidelines for RCC, commonly recommended first-line treatments for patients with a good/intermediate prognosis include bevacizumab + IFN-α, sunitinib, and pazopanib.[9,10] Other ESMO-recommended first-line treatments include sorafenib, high-dose IL-2, and low-dose IFN-α + bevacizumab. RCC patients with a poor prognosis typically receive temsirolimus, although sunitinib, pazopanib, and sorafenib are potential options.[9] Treatment options for patients in the second line include axitinib, sorafenib, and pazopanib following cytokine treatment, and axitinib and everolimus following treatment with a TKI; sorafenib is also an option following TKI treatment.[9,10] Updated 2016 treatment guidelines from the National Comprehensive Cancer Network (NCCN)[11] recommend nivolumab, lenvatinib, or cabozantinib as subsequent treatment after first-line therapy, based on positive results comparing the three treatments to everolimus in Phase II/III trials.[6,8,12]

There is a lack of head-to-head trial data comparing these second- or later-line treatment options, especially since the few trials that addressed this used a variety of comparators, such as placebo, everolimus, and sorafenib. Therefore, it is difficult to understand the comparative efficacy and safety of these newer drugs (e.g., nivolumab, lenvatinib, and cabozantinib), and how these compare to more established treatments.

To provide practice guidance into the rapidly expanding treatment landscape for advanced RCC, a network meta-analysis (NMA) was conducted to determine the efficacy and safety of sorafenib in relation to other established and investigational agents in second- and later-lines of therapy.

Materials and Methods

Literature Identification We systematically searched for randomized controlled trials (RCTs) indexed in Embase

Keywords: Renal cell carcinoma, network meta-analysis

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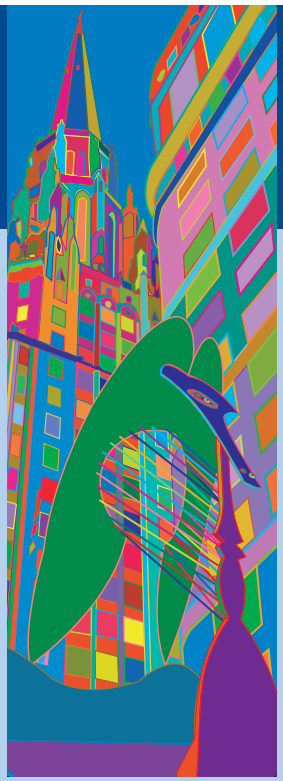

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Table 1: Inclusion/Exclusion Criteria

	Inclusion Criteria	Exclusion Criteria
Population	Adults (≥18 years old) with advanced or metastatic RCC, enrolled in RCTs with ≥50 patients enrolled in each treatment arm	Studies that do not evaluate the population of interest
Intervention/ Comparators	• Targeted therapies and/or chemotherapies used in any line • Monotherapy and/or combination therapy	• Adjuvant therapies • Non-pharmacologic therapies • Palliative care
Outcomes	• CBR • PFS • OS • Dose reduction due to adverse events • Treatment discontinuations due to any cause	• Studies that do not report outcomes of interest for the study population
Study Design	• Phase II/III RCTs	• Animal, in vitro, or genetic studies, reviews, case reports, editorials, non-randomized observational studies

Abbreviations: CBR = clinical benefit rate; OS = overall survival; PFS = progression-free survival; RCC = renal cell carcinoma; RCT = randomized controlled trial

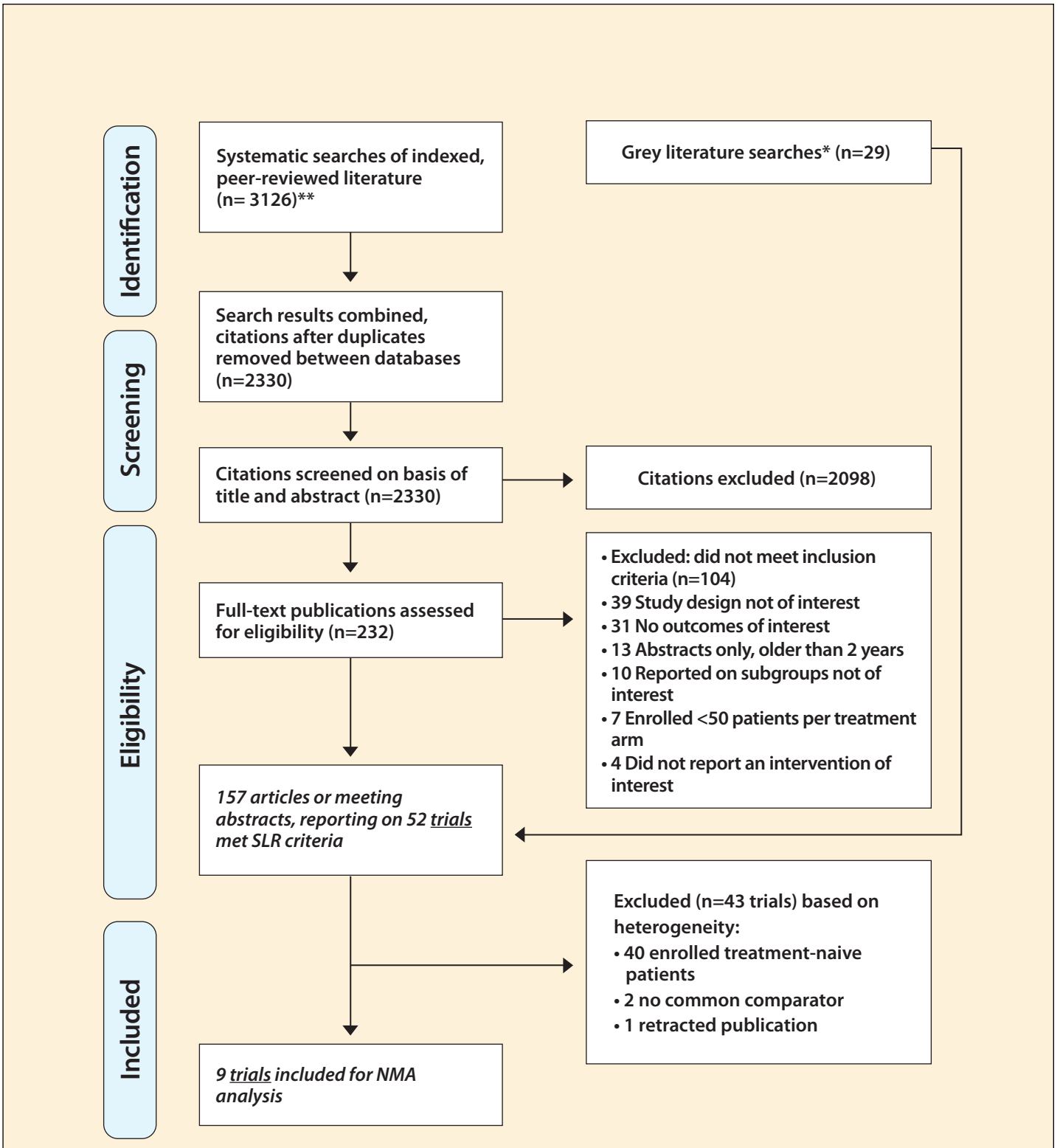
and PubMed. These bibliographic databases were accessed on January 5, 2016 to identify English-language studies published since January 1, 2004. A search strategy was developed using terms to specifically identify trials in advanced RCC. The search algorithm was not limited to any particular treatments, so that new investigational therapies could also be captured. The search was validated by cross-referencing the results against the bibliographies of published systematic reviews. Recent abstracts from major clinical oncology and urology meetings were reviewed to identify any Phase II/III trials that had not yet been published (i.e., "grey" literature).

Study Selection and Data Extraction All identified abstracts were reviewed against the inclusion and exclusion criteria described in **Table 1**. RCTs of patients with advanced or metastatic RCC that compared targeted therapy and/or chemotherapy alone or in combinations were included. The full texts of studies that passed abstract screening were evaluated using the same criteria. To limit the results to studies with more precise estimates of treatment effects and higher statistical power, trials were excluded if they enrolled fewer than 50 patients per treatment arm. Data elements extracted from each included study were study design, patient and treatment characteristics, and clinical efficacy and safety outcomes.

Feasibility Assessment A feasibility assessment was conducted to determine whether the identified trials provided data suitable for an NMA. This assessment sought to determine the selection of trials that presented sufficient data for generating an evidence network for each outcome of interest. The assessment also ensured that there were minimal systematic differences in patient or disease characteristics (clinical heterogeneity) for factors that may influence the comparability of relative results (treatment effect modifiers).

Analysis Fixed-effects Bayesian NMAs were used to conduct indirect comparisons of the included trials for each of the outcomes of interest. Efficacy outcomes were progression-free survival (PFS), overall survival (OS), and the proportion of patients with clinical benefit, which is defined as complete response, partial response, or stable disease per the Response Evaluation Criteria in Solid Tumors (RECIST). Safety outcomes included the proportion of patients with treatment discontinuations due to any cause, and the proportion of patients with one or more dose reductions due to adverse events. PFS and OS were analyzed as hazard ratios (HRs) with Bayesian 95% credible intervals (CrI). The Bayesian 95% CrI has the interpretation that, given the clinical and statistical assumptions made, there is a 95% chance that the mean falls within the CrI noted. CBR and the safety outcomes evaluated proportions of patients and were analyzed as odds ratios (ORs). For discussion purposes, 95% CrIs that do not include '1' are considered "statistically significant". Analyses were con- ducted in OpenBUGS 3.2.2 with a 50,000 run-in iteration phase and a 50,000-iteration phase for parameter estimation. Because no two trials in the network evaluated the same two treatments, statistical heterogeneity could not be assessed and random-effects models were not employed.

Two sensitivity analyses with modified networks were conducted to explore the impact of prior therapies and study design on the results. These analyses included: (1) network modification to evaluate the mammalian target of rapamycin (mTOR) inhibitors (everolimus and temsirolimus) as single therapies (i.e., introducing the assumption that these two therapies have equivalent treatment effects); and (2) within this network from the first sensitivity analysis, the exclusion of studies that enrolled only patients treated previously with only cytokines—to capture a population more representative of the current treatment landscape.



Abbreviations: RCT = Randomized controlled trial; SLR = Systematic literature review

*Specified conference proceedings were searched for the most recent year to supplement the peer-reviewed literature.

**Includes total hits from both Published and Embase database searches.

Figure 1: Study Attrition Diagram for Systematic Literature Review

Table 2: Summary of Trial Characteristics

		Type of Prior Therapy			Baseline Characteristics		Outcomes Reported				
Author, Year, Trial	Intervention and Comparator	VEGF	mTOR	Cytokines	ECOG Performance Status 0; 1; 2 (%)	MSKCC Prognostic Risk Favorable; Intermediate; Poor (%)	CBR	PFS	OS	Discontinu-ations	Dose Reductions
Motzer et al, 2014. GOLD (NCT01223027)[18]	Dovitinib (n= 284) Sorafenib (n= 286)	100%	100%	7%–8%	NR	20%; 58%; 22% 21%; 57%; 23%	✓	✓	✓	✓	✓
Motzer et al, 2010. RECORD-1 (NCT00410124)[12]	Everolimus (n= 277) Placebo (n= 139)	100%	0%	IFN: 51%–52% IL2: 24%–22%	NR	29%; 56%; 15% 28%; 57%; 15%	✓	✓	✓	✓	✓
Escudier et al, 2009. TARGET (NCT00073307)[19]	Sorafenib (n= 451) Placebo (n= 452)	0%	0%	81%–83%	49%; 49%; 2% 46%; 52%; 1%	51%; 49%; 0% 49%; 49%; 0%	✓	✓	✓	✓	✓
Sternberg et al, 2013. VEG105192 (NCT00334282)[20]	Pazopanib (n= 135) Placebo (n= 67)	0%	0%	100%	42%; 58%; 0% 41%; 59%; 0%	39%; 55%; 3% 39%; 53%; 3%	✓	✓	✓		
Rini et al, 2011. AXIS (NCT00678392)[21]	Axitinib (n= 596) Sorafenib (n= 599)	62%	3%	35%	54%; 45%; <1% 55%, 44%; 0%	28%; 37%; 33% 28%; 36%; 33%	✓	✓	✓	✓	
Hutson et al, 2014. INTORSECT (NCT00474786)[22]	Temsirolimus (n= 259) Sorafenib (n= 253)	100%	NR	NR	40%; 58%; 2% 45%; 55%; <1%	19%; 69%; 12% 17%; 70%; 13%	✓	✓	✓	✓	✓
Motzer et al, 2015. (NCT01136733)[5]	Lenvatinib+everolimus (n= 51) Lenvatinib (n= 52) Everolimus (n= 50)	100%	NR	18%	NR	NR		✓	✓		
Choueiri et al, 2015. METEOR (NCT01865747)[7]	Cabozantinib (n= 187) Everolimus (n= 188)	100%	0%	IL-2: 6–9% IFNα: 3-7%	69%; 31%; 0% 62%; 38%; 0%	43%; 43%; 14% 44%; 40%; 16%	✓	✓	✓	✓	
Motzer et al, 2015. CHECKMATE025 (NCT01668784)[3]	Nivolumab (n= 410) Everolimus (n= 411)	100%		NR	NR	35%; 49%; 16% 36%; 49%; 15%	✓	✓	✓	✓	

Abbreviations: CBR = clinical benefit rate; ECOG = Eastern Cooperative Oncology Group; MSKCC = Memorial Sloan Kettering Cancer Center; mTOR = Mammalian target of rapamycin inhibitors; NR = Not reported; PFS = Progression free survival; OS = Overall survival; VEGF = Vascular endothelial growth factor inhibitors.

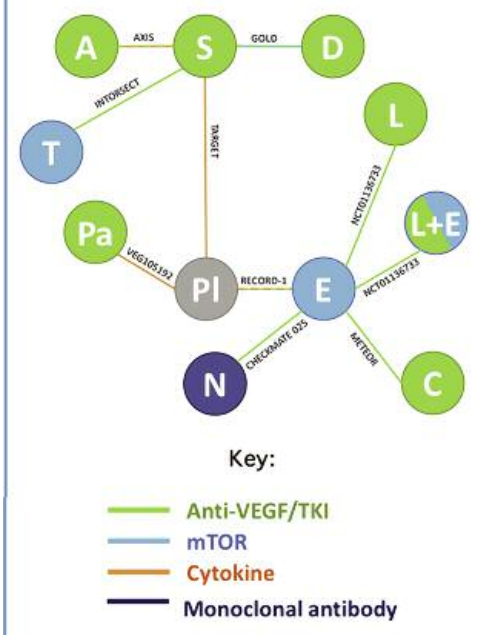
Results

Study Eligibility and Characteristics **Figure 1** depicts the flow diagram of the systematic literature search and RCT selection. The search identified 2,230 abstracts, of which 157 publications—representing 52 unique RCTs—investigated treatment of advanced or metastatic RCC, reported outcomes of interest, and were eligible for inclusion in the NMA. These 52 trials were then evaluated in the feasibility assessment for clinical heterogeneity and their ability to contribute to quantitative analyses.

The feasibility assessment determined that the included studies were heterogeneous with regards to previous treatment, so analyses were limited to trials evaluating therapies in second- or later-line settings; studies involving patients who were treatment-naïve for advanced or metastatic disease were excluded. Given that the therapeutic landscape has been changing rapidly over the last decade, we considered the potential impact of the date/year of patient enrollment as a source of heterogeneity between trials, as different targeted therapies came to market. Notably, the addition of new agents to the therapeutic landscape as well as increasing experience of the treating oncologists from 2005 to the present (the TKI era), has led to better clinical outcomes.[13-17] We observed that the number and type of prior therapies (cytokine therapy, vascular endothelial growth factor [VEGF] and mTOR inhibitors) were sources of potential heterogeneity across trials. Similarly, we observed variations in trial enrollment by Memorial Sloan Kettering Cancer Center (MSKCC) risk score. The analysis results should be interpreted in the context of such differences among trials (**Table 2**).

Overall, the feasibility assessment concluded that nine trials could contribute data for the outcomes of interest to

Table 3: Base-Case Indirect Comparison of Sorafenib to Other Targeted Therapies for Efficacy and Safety Outcomes



Sorafenib versus...	CBR OR [95% CrI]	PFS HR [95% CrI]	OS HR [95% CrI]	Dose Reductions OR [95% CrI]	Treatment Discontinuations OR [95% CrI]
		Efficacy Outcomes		Safety Outcomes	
Placebo	4.27 [3.14, 5.84]	0.44 [0.35, 0.55]	0.88 [0.74, 1.04]	**4.78 [2.69, 9.23]**	0.58 [0.44, 0.78]
Axitinib	**0.52 [0.38, 0.70]**	**1.50 [1.23, 1.84]**	1.03 [0.85, 1.25]	**2.48 [1.82, 3.36]**	**1.62 [1.18, 2.22]**
Cabozantinib	**0.36 [0.17, 0.75]**	**2.30 [1.48, 3.58]**	1.50 [0.97, 2.34]	1.60 [0.07, 11.60]	**3.32 [1.11, 12.28]**
Dovitinib	1.01 [0.73, 1.41]	1.16 [0.97, 1.40]	1.04 [0.82, 1.33]	----	0.81 [0.48, 1.34]
Everolimus	0.93 [0.53, 1.57]	1.33 [0.94, 1.91]	1.01 [0.72, 1.41]	0.34 [0.01, 2.38]	**7.56 [2.66, 27.49]**
Lenvatinib	----	**2.19 [1.21, 3.98]**	----	----	----
Lenvatinib + everolimus	----	**3.34 [1.77, 6.32]**	1.84 [0.91, 3.69]	----	----
Nivolumab	0.97 [0.52, 1.75]	**1.51 [1.03, 2.24]**	1.38 [0.91, 2.09]	----	**19.93 [6.27, 78.34]**
Pazopanib	----	0.82 [0.50, 1.34]	1.07 [0.72, 1.58]	----	----
Temsirolimus	1.00 [0.69, 1.45]	1.15 [0.94, 1.41]	0.76 [0.61, 0.95]	**2.58 [1.69, 3.98]**	1.38 [0.47, 4.30]

Abbreviations: CBR = clinical benefit rate; CrI = Credible interval; HR = Hazard ratio; OR = Odds ratio; OS = Overall survival; PFS = Progression free survival

Bolded text indicates that the CrI does not cross the line of no effect (i.e., statistically significant). Blue text indicates that the point estimate favors sorafenib.

an NMA of second- or later-line therapies for advanced or metastatic RCC. The nine RCTs consisted of a total of 5,147 patients in 21 different treatment arms, including sorafenib, axitinib, cabozantinib, dovitinib, everolimus, temsirolimus, lenvatinib, lenvatinib + everolimus, nivolumab, pazopanib, and placebo. **Table 3** summarizes the base-case results of the NMA. **Table 4** summarizes the results of the different sensitivity analyses.

Clinical Benefit Rate Treatment with sorafenib resulted in a CBR that was significantly higher than that for placebo, and very similar to rates for dovitinib, everolimus, nivolumab, and temsirolimus (**Table 3**). The odds of clinical benefit were approximately four times greater for sorafenib compared to placebo; however, axitinib and cabozantinib were associated with a significantly greater likelihood of clinical benefit than sorafenib—approximately two and three times greater, respectively. The width of the CrIs associated with these comparisons suggests that the estimation of comparative effect is acceptably precise.

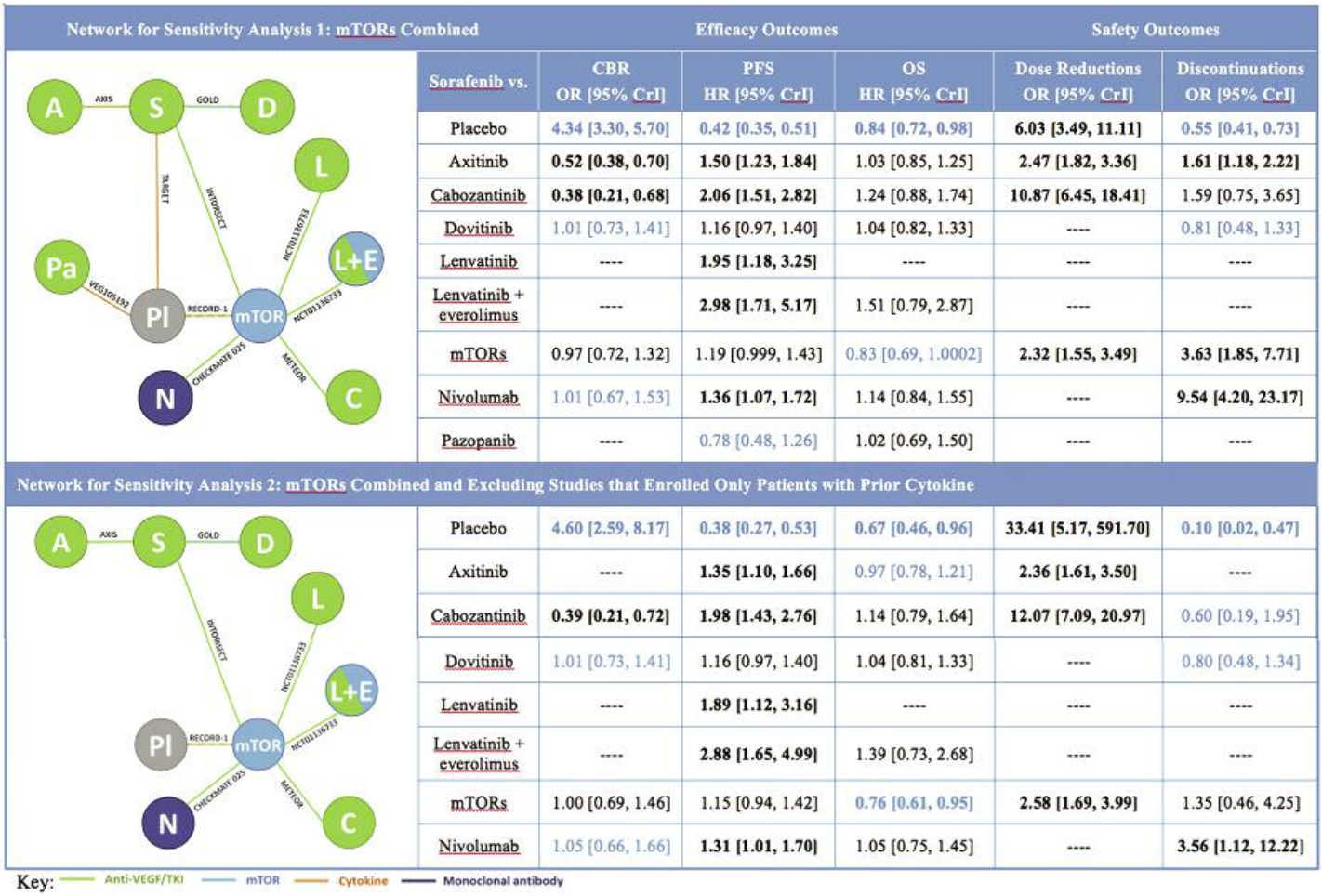
The results of the sensitivity analyses for CBR did not differ substantively from the base-case analysis (**Table 4**). There were no changes in significance, and the overall magnitude of difference was minimal in each sensitivity analysis. The similarity between the base-case and these sensitivity analyses is likely due to the similar effect of temsirolimus and everolimus on CBR. As we see in the base-case analyses, temsirolimus and sorafenib were equally likely to produce clinical benefit (OR [95% CrI]: 1.00 [0.69, 1.45]), and the results for everolimus were nearly identical (OR [95% CrI]: 0.93 [0.53, 1.57]). These results are in line with the assumption that mTOR inhibitors should be considered functionally and clinically equivalent to each other, with respect to CBR.

Progression-free Survival Sorafenib was associated with significantly longer PFS compared with placebo and exhibited similar PFS compared with dovitinib, pazopanib, and temsirolimus. Although this was not statistically significant, sorafenib therapy demonstrated a net improvement in PFS compared to pazopanib (HR [95% CrI]: 0.82 [0.50, 1.34]). Everolimus showed somewhat longer PFS than sorafenib, but the analysis was not statistically significant.

Several TKIs—axitinib, cabozantinib, lenvatinib (as

Table 4: Impact of Variations in Network Characteristics on Indirect Comparisons of Sorafenib to Other Targeted Therapies

Network for Sensitivity Analysis 1: mTORs Combined	Efficacy Outcomes			Safety Outcomes	
Sorafenib vs.	CBR OR [95% CrI]	PFS HR [95% CrI]	OS HR [95% CrI]	Dose Reductions OR [95% CrI]	Discontinuations OR [95% CrI]
Placebo	4.34 [3.30, 5.70]	0.42 [0.35, 0.51]	0.84 [0.72, 0.98]	**6.03 [3.49, 11.11]**	0.55 [0.41, 0.73]
Axitinib	**0.52 [0.38, 0.70]**	**1.50 [1.23, 1.84]**	1.03 [0.85, 1.25]	**2.47 [1.82, 3.36]**	**1.61 [1.18, 2.22]**
Cabozantinib	**0.38 [0.21, 0.68]**	**2.06 [1.51, 2.82]**	1.24 [0.88, 1.74]	**10.87 [6.45, 18.41]**	1.59 [0.75, 3.65]
Dovitinib	1.01 [0.73, 1.41]	1.16 [0.97, 1.40]	1.04 [0.82, 1.33]	----	0.81 [0.48, 1.33]
Lenvatinib	----	**1.95 [1.18, 3.25]**	----	----	----
Lenvatinib + everolimus	----	**2.98 [1.71, 5.17]**	1.51 [0.79, 2.87]	----	----
mTORs	0.97 [0.72, 1.32]	1.19 [0.999, 1.43]	0.83 [0.69, 1.0002]	**2.32 [1.55, 3.49]**	**3.63 [1.85, 7.71]**
Nivolumab	1.01 [0.67, 1.53]	**1.36 [1.07, 1.72]**	1.14 [0.84, 1.55]	----	**9.54 [4.20, 23.17]**
Pazopanib	----	0.78 [0.48, 1.26]	1.02 [0.69, 1.50]	----	----
Network for Sensitivity Analysis 2: mTORs Combined and Excluding Studies that Enrolled Only Patients with Prior Cytokine					
Placebo	4.60 [2.59, 8.17]	0.38 [0.27, 0.53]	0.67 [0.46, 0.96]	**33.41 [5.17, 591.70]**	0.10 [0.02, 0.47]
Axitinib	----	**1.35 [1.10, 1.66]**	0.97 [0.78, 1.21]	**2.36 [1.61, 3.50]**	----
Cabozantinib	**0.39 [0.21, 0.72]**	**1.98 [1.43, 2.76]**	1.14 [0.79, 1.64]	**12.07 [7.09, 20.97]**	0.60 [0.19, 1.95]
Dovitinib	1.01 [0.73, 1.41]	1.16 [0.97, 1.40]	1.04 [0.81, 1.33]	----	0.80 [0.48, 1.34]
Lenvatinib	----	**1.89 [1.12, 3.16]**	----	----	----
Lenvatinib + everolimus	----	**2.88 [1.65, 4.99]**	1.39 [0.73, 2.68]	----	----
mTORs	1.00 [0.69, 1.46]	1.15 [0.94, 1.42]	0.76 [0.61, 0.95]	**2.58 [1.69, 3.99]**	1.35 [0.46, 4.25]
Nivolumab	1.05 [0.66, 1.66]	**1.31 [1.01, 1.70]**	1.05 [0.75, 1.45]	----	**3.56 [1.12, 12.22]**



Abbreviations: CBR = clinical benefit rate; CrI = Credible interval; HR = Hazard ratio; mTOR = Mammalian target of rapamycin; OR = Odds ratio; OS = Overall survival; PFS = Progression free survival.

Bolded text indicates that the CrI does not cross the line of no effect (i.e., statistically significant). Blue text indicates that the point estimate favors sorafenib.

well as lenvatinib in combination with everolimus), and nivolumab—showed significantly longer PFS compared with sorafenib. The PFS hazard rates for sorafenib ranged from 50% to almost three-and-a-half times larger than the rates of these comparators. No substantive differences were seen in the sensitivity analyses for PFS.

Overall Survival Base-case OS comparisons are reported in **Table 3**. Comparisons of sorafenib with other agents yielded hazard ratios that ranged from 0.76–1.84; however, none of these comparisons were statistically significant, except for sorafenib resulting in statistically significantly longer OS compared with temsirolimus. OS for sorafenib and everolimus was nearly identical (OR [95% CrI]: 1.01 [0.72, 1.41]), but the sensitivity analyses that combined mTOR inhibitors and restricted to studies with prior angiogenesis inhibitors exhibited results that were almost the same as the results seen for temsirolimus in the base case.

In the sensitivity analyses (**Table 4**), there was no change in the direction, statistical significance, or material difference in the magnitude of the relative estimates of comparison between sorafenib and other therapies with regard to OS. When analyzed as a class, mTORs had a slightly shorter OS compared with sorafenib (HR: 0.83), falling between the estimates for temsirolimus (HR: 0.76) and everolimus (HR: 1.01) in the base case.

Dose Reductions Sorafenib was associated with significantly greater odds of dose reduction due to adverse events versus placebo, axitinib, and temsirolimus (**Table 3**). Similarly, the odds of dose reduction were higher for sorafenib when compared to cabozantinib, and this finding became significant with a modified network. In contrast, the OR for dose reduction was numerically lower for sorafenib when compared with everolimus (OR [95% CrI]: 0.34 [0.01, 2.38]).

When evaluating mTORs as a class with a modified network (**Table 4**), the OR for mTORs (2.32), fell between the base-case estimates for everolimus (0.34) and temsirolimus (2.58). When the trials evaluating only cytokine-pretreated patients were removed (the second

sensitivity analysis), the connection between sorafenib and mTOR was based solely on the INTORSECT trial[22] of temsirolimus; thus, the estimate reverted back to the base-case estimate for temsirolimus (2.58). Because the METEOR trial[8] compared cabozantinib to everolimus, the comparison of cabozantinib to sorafenib in the sensitivity analyses was influenced by the performance of temsirolimus. As the OR for sorafenib versus the mTORs increased in the sensitivity analyses, the OR of sorafenib versus cabozantinib correspondingly increased; in the base case, the OR was 1.60, and in the sensitivity analyses rose to statistically significant ORs of 10.87 (#1) and 12.07 (#2).

In some cases, the CrIs for the analyses of dose reductions were notably wide (i.e., indicating a low level of precision for the estimates), due to a low number of patients reducing doses in some trials. This was particularly true for the placebo arms of trials, where, for example, only one patient who received placebo in the RECORD-1 trial[12] had a dose reduction. In the second sensitivity analysis (which removes trials that enrolled only cytokine-pretreated patients), the comparison of sorafenib and placebo relied on the RECORD-1 trial[12] rather than the TARGET trial,[19] leaving the resulting estimate highly unstable (OR [95% CrI]: 33.41 [5.17, 591.70]).

Treatment Discontinuations Sorafenib was associated with significantly decreased odds of treatment discontinuation compared with placebo. Sorafenib was also associated with greater odds of treatment discontinuation compared to axitinib, cabozantinib, everolimus, temsirolimus, and nivolumab; however, the results of the comparison to temsirolimus were not statistically significant.

As with the analysis of dose reductions, the network modifications relied more heavily on temsirolimus for the estimated effect of sorafenib compared to the mTORs and, by extension, to cabozantinib and nivolumab, which were compared to (and connect to the network through) everolimus. The sensitivity analyses consistently found that the differences between therapies were reduced, particularly for the comparisons of sorafenib with cabozantinib and nivolumab.

Discussion

For CBR and PFS, sorafenib performed better than placebo and similar to dovitinib and the two mTORs, everolimus and temsirolimus. In addition, while there was an advantage for nivolumab for PFS, there was no significant or substantive difference between nivolumab and sorafenib with regard to CBR. Sorafenib performed worse than axitinib, cabozantinib, and both monotherapy and combination therapy involving lenvatinib.

For OS, many of the differences between sorafenib and other treatments were attenuated or disappeared. Sorafenib performed better than placebo and was substantively equivalent (i.e., an HR close to 1) to all other treatments with the exception of the newer agents, cabozantinib, nivolumab, and lenvatinib + everolimus. This may be an inherent bias in the time-dependent analysis favoring the three new agents since OS has been improving since 2005 as more drugs become available; patients were generally poorer risk in the early TKI era and physicians have become more skilled at using all the drugs at their disposal. In addition, in the sensitivity analysis in which the two mTORs were assumed equivalent and involving studies excluding patients exposed to only cytokines, the substantive differences with cabozantinib and nivolumab disappeared (HRs = 1.14 and 1.05, respectively).

For safety outcomes, there was more variation across the base-case and sensitivity analyses. The only general conclusion to be made is that dose reductions and treatment discontinuations were more common on sorafenib than most other treatments, which may be related to stomatitis and hand-foot syndrome.

While an association between PFS and OS has been observed for some treatments for advanced RCC, researchers have cautioned against using PFS as a surrogate endpoint for OS. Becker et al. observed that the net benefit of PFS is not often seen in OS and that more careful examination of subsequent therapies (both in those studies showing an association and those not) is warranted.[23] Given that PFS and CBR are less clinically relevant to patients and providers than OS, that OS is a bedrock of regulatory approval, and that comparisons of sorafenib with other agents yielded non-significant differences in OS (hazard ratios 0.76–1.84), the role of sorafenib in the treatment sequencing of metastatic RCC should be re-considered. These results underscore what many clinicians believe, namely that sorafenib is active yet widely underused mostly due to low-grade chronic toxicities and a perception of poorer survival outcomes. We here demonstrate that OS endpoints with sorafenib are not dramatically different from the newer agents. The bias against sorafenib may well be time-dependent. It was the first agent approved for metastatic RCC, and physicians were inexperienced in managing toxicities and had few options to use to improve survival when sorafenib failed. Moreover, the prolonged OS results seen with the newer agents reflect in part the benefit of subsequent therapies, including in some cases sorafenib.[24,25]

There were two main limitations for the analysis. The first is the sparsity of the network; most connections between treatments were based on the results of only one study; thus, it was impossible to estimate statistical heterogeneity. Based on differences across studies, potential sources of clinical heterogeneity were the number and type of prior therapies (cytokine therapy, VEGF, and mTOR inhibitors) and baseline MSKCC risk score. While these differences were generally minor, the older studies (which were also studies that enrolled patients with only prior cytokine therapy) such as TARGET and VEG105192, enrolled more patients with poorer risk; assuming that these differences impact the relative effects of treatment, this could have introduced bias into the base-case analy-

ses and is explored in the second sensitivity analysis. Between the clinical heterogeneity present and the lack of ability to estimate statistical heterogeneity, generalizations from the extant literature on these questions are limited.

The second limitation, somewhat connected to the first, concerns the equivalence (or not) of mTORs. To explore any bias introduced by including trials enrolling patients with only prior cytokines, the mTORs were assumed equivalent in the sensitivity analyses so as to retain a connected evidence network. While there is some suggestion they may be similar (i.e., that the molecules differ structurally only in an ester moiety) the difference in results we found for dose reduction and discontinuations suggest that this may not be the case. For the safety analyses in particular, we can conclude that there is some heterogeneity; however, because there are at least three sources of bias (receipt of prior cytokines in the base case, combining mTORs in the sensitivity analyses, and time-dependent physician experience with the drugs) it is not possible to fully account for the differences.

Conclusion

The results of this network meta-analysis show that OS is nearly identical for sorafenib and a number of comparators, including axitinib, dovitinib, everolimus, pazopanib, and, in sensitivity analysis, cabozantinib, and nivolumab, as well. This result is supported by another published meta-analysis in which sorafenib showed a significantly better OS than temsirolimus.[25] However, sorafenib had more dose reductions and discontinuations compared with newer treatments (usually related to stomatitis and hand foot syndrome, two toxicities that are still resistant to supportive care interventions), but had comparable efficacy to the mTOR inhibitors, everolimus and temsirolimus. These results suggest that in resource-restricted environments, health authorities should require that high-cost newer agents, such as cabozantinib and nivolumab, be compared in Phase III trials to sorafenib, a lower-cost older agent, before approving the newer agents.

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A Recap of Key Findings Offers 'Reality Check' on Essential Data, Trends

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If clinicians were looking for a signal to identify future directions and potential destinations in kidney cancer care and research, they might orient themselves with highlights from this year's ASCO GU meeting. There was an abundance of new data, not much shattering, but noteworthy and intriguing, possibly setting the stage for inflection points yet to emerge.

(Editor's note: All abstracts from the meeting can be viewed at this website: http://meetinglibrary.asco.org/abstractbysubcategory/2017%20Genitourinary%20Cancers%20Symposium/40)

One of the big stories to emerge from the 2017 GU ASCO Scientific Sessions in Orlando, aside from an exciting agenda packed with a broad spectrum of findings, was the size of the meeting itself. From its relatively modest origins 10 years ago, this meeting has mushroomed exponentially. Attendance has soared from that first event when 1,450 attendees came to the venue to this year's 3,300. That first meeting was described as small, accessible, and comfortable, allowing for "a more intimate setting for the practicing oncologist," according to one account on ASCO's website. With several thousand in attendance, that description may be debatable as the GU sessions become one of the major oncologic meetings worldwide.

Although it lacks the panache and attention given to the annual ASCO meeting in June, the GU sessions offer a striking opportunity for clinicians to catch up on specific trends in renal cell carcinoma (RCC) likely to evolve over the next few years, trends that could foreshadow results that may be presented at ASCO's flagship meeting in Chicago. Among the standout abstracts and presentations from the 2017 sessions were:

- Intermediate-term outcomes from the DISSRM registry: a prospective analysis of active surveillance in patients with small renal masses. (Abstract 430, Ridwan A, et al.)
- A phase 2 study of atezolizumab with or without bevacizumab versus sunitinib in untreated metastatic RCC patients. (Abstract 431, McDermott DF, et al.)
- Evolution of circulating tumor DNA profile from first-line to second-line therapy in metastatic RCC. (Abstract 434, Pal SK et al.)
- Outcomes of PD-1/PD-L1 responders who discontinue therapy for immune-related adverse events (ir-AEs) results of a cohort of patients with metastatic RCC. (Abstract 467, McKay RR et al.)
- Pembrolizumab plus low-dose ipilimumab for patients with advanced RCC: Phase 1 KEYNOTE-029 study. Abstract 510, Choueiri TK, et al.)

Intermediate-term outcomes from the DISSRM Registry (Abstract 430).

The goal of active surveillance as an alternative to primary intervention is to reduce the overtreatment of small renal masses, defined as solid renal masses ≤4.0 cm (clinical stage T1a). Since 2009, the Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) registry prospectively enrolled 615 patients with small renal masses who chose to undergo primary intervention or active surveillance. Intervention was recommended to patients for masses with a rapid growth rate (0.5 cm/year) or increased tumor diameter (>4.0 cm). Primary outcomes were cancer-specific survival and overall survival; secondary outcomes included progression-free survival. Progression was strictly defined as a growth rate of 0.5 cm/year, greatest tumor diameter over 4.0 cm, new onset metastatic disease, or elective crossover.

Of the 615 enrolled patients, 298 (48.5%) chose primary intervention and 317 (51.5%) chose active surveillance. From the active surveillance cohort, 45 (14.2%) patients underwent delayed intervention. Median follow-up time for the entire registry was 2.9 years, with 203 (33.0%) patients followed for 5 years or more.

Ridwan et al found no difference in cancer-specific survival at 7 years between primary intervention and active surveillance (99.0% vs. 100%, respectively, p = 0.3). However, overall survival was higher in patients with primary intervention when compared to active surveillance at 5 years (93.0% vs. 80.2%, respectively) and 7 years (91.7% vs. 65.9%, respectively, p = 0.002). The 5-year and 7-year progression free survival rate in the active surveillance cohort was 76.7% and 48.4%, respectively.

This study helps clarify the extent to which active surveillance may be an effective strategy in the intermediate term for patients with small renal masses. In the intermediate term, active surveillance appears to be as effective as primary intervention from a cancer-specific survival for carefully selected patients with small renal masses. As cancer-specific survival appears to be similar in the intermediate term, the overall survival difference can be attributed to selection bias and patient comorbidities. As the registry matures, further studies will elucidate the outcomes of active surveillance in the long term. Clinical trial information can be found at NCT02346435.

■ A novel immunotherapy combination (atezolizumab + bevacizumab) vs sunitinib (Abstract 431).

One of the major obstacles to overcome with the use of VEGF-directed therapy is the resistance that invariably develops, often within the first year. With more attention focused on the use of immune checkpoint blockade there is keen interest in whether anti PD-L1 therapy can improve efficacy while still achieving an acceptable safety profile. McDermott et al evaluated the safety of a novel combination of atezolizumab (anti-PD-L1) with bevacizumab (anti-VEGF); it was compared with atezolizumab monotherapy and with sunitinib (TKI) in first-line mRCC.

Treatment-naive mRCC patients were randomized to one of 3 arms: atezolizumab 1200 mg IV q3w + bevacizumab 15 mg/kg IV q3w, atezolizumab alone, or sunitinib 50 mg PO daily 4 weeks on/2 weeks off. Crossover to the combination arm after disease progression was allowed for patients receiving atezolizumab alone or sunitinib. Median follow up was 20.7 months. The PFS HR in ITT pts was 1.00 for atezolizumab + bevacizumab vs sunitinib and 1.19 for atezolizumab vs sunitinib. In PD-L1+ patients, the PFS HR was 0.64 for atezolizumab + bevacizumab vs sunitinib and 1.03 for atezolizumab vs sunitinib. Treatment-related Grade 3-4 adverse events (AEs) were seen in 40%, 16% and 57% of patients in the atezolizumab + bevacizumab, atezolizumab, and sunitinib arms, respectively. AEs leading to death occurred in 3%, 2% and 2% of pts, respectively.

This is a phase 2 study and the phase 3 results of the novel combination are eagerly awaited. Atezolizumab + bevacizumab resulted in encouraging antitumor activity in the PD-L1+ subgroup of first-line RCC patients. Furthermore, the safety profile of atezolizumab + bevacizumab is consistent with the known profile of each drug when considered separately, although the high rate (40%) of grade 3-4 AEs is not insignificant. In PD-L1 positive patients there was favorable efficacy data. The clinical benefit of atezolizumab + bevacizumab vs sunitinib will be evaluated in the ongoing Phase 3 study IMmotion151 (NCT02420821). Clinical trial information on the ASCO GU data can be found at NCT01984242.

■ Are there potential implications with the evolution of circulating tumor DNA (ctDNA) profile from first-line to second-line therapy in metastatic renal cell carcinoma (mRCC)? (Abstract 434)

Pal et al examined circulating tumor DNA (ctDNA) from patients undergoing first-line and second-line therapy. The authors studied whether these changes could ultimately impact therapeutic choices. Treatment of mRCC typically involves mechanistically distinct agents across the first and second line settings. ctDNA provides a promising platform to conveniently investigate temporal changes in overall genomic profiles of patients undergoing systemic therapy.

Data were obtained from patients with mRCC who underwent ctDNA profiling as a part of routine clinical care at progression using a CLIA-certified platform evaluating 70 genes. Genomic alterations (GAs) were pooled for the entire cohort. A comparison of first line (1L) vs. second line (2L) setting was performed, with grouping based on conventional practice patterns (1L regimens included sunitinib, pazopanib and bevacizumab, and 2L regimens included everolimus, axitinib, cabozantinib, and nivolumab). ctDNA results from 224 pts with mRCC were assessed (89 clear cell, 37 non-clear cell, 98 unknown). GAs were detected in 78.6% of patients. The most frequent GAs in the overall cohort included *TP53* (35%), *VHL* (23%), *EGFR* (17%), *NF1* (16%), and *ARID1A* (12%). 64 and 56 patients received 1L and 2L agents, respectively. The average number (range) of ctDNA alterations detected was 2.9 (1-14) in 1L and 3.7 (1-16) in 2L with median (range) ctDNA variant allele fractions of 0.23 (0.05-9.92) in 1L and 0.24 (0.04-47.14) in 2L. The highest disparity in GA frequencies in 2L vs. 1L were in *TP53* (49% vs. 25%), *VHL* (29% vs. 25%), *NF1* (20% vs. 15%), *EGFR* (17% vs. 21%), and *PIK3CA* (17% vs. 8%). Isolating 2L patients who specifically received 1L VEGF-therapy, these differences were even more prominent in comparison to 1L pts: *TP53* (64% vs. 31%), *PIK3CA* (29% vs. 8%), and *NF1* (29% vs. 4%).

This report is the largest assessment of ctDNA in mRCC to date; the majority of patients demonstrating clinically relevant GAs. Increasing p53 and mTOR pathway (e.g, NF1, PIK3CA) alterations in 2L patients who received 1L VEGF-directed therapy may help elucidate mechanisms of 1L therapy resistance. Increasing GA frequency from 1L to 2L patients may have implications for immunotherapeutic approaches. Interestingly, the rate of *TP53* mutations in this cohort is surprisingly high. While ctDNA offers an easily accessible means to study genomic alterations, and a potential method to assimilate intratumoral heterogeneity, these results still need to be vali-

dated in additional patient cohorts, and using different ctDNA platforms.

■ Immune-related adverse events/outcomes of PD-1/PD-L1 responders who discontinue therapy early. (Abstract 467)

Early findings from a new study appear to challenge the current standard practice for immune checkpoint inhibitor therapy—continuing treatment until cancer worsens. Among patients with advanced kidney cancer who stopped anti-PD-1/PD-L1 immunotherapy early due to adverse events, 42% had a durable response, meaning they were able to remain off additional systemic therapy for 6 months or more. More broadly, this insight may help alleviate some patients' concerns about the impact of discontinuing immunotherapy. Although there have been prior anecdotal data hinting at this possibility, the authors note that this is the first study evaluating the outcomes of patients with metastatic renal cell carcinoma who stop anti-PD-1/PD-L1 therapy due to adverse events. While this is a small case series, with findings that need validation in a larger group of patients, it underscores that in some cases, immunotherapy can have lasting benefits—even beyond treatment discontinuation.

The analysis included 19 patients with mRCC that responded to immune checkpoint inhibitor therapy. The majority (63%) received anti-PD-1/PD-L1 therapy as a stand-alone treatment; 37% received anti-PD-1/PD-L1 inhibitors in combination with other systemic treatments. The median time on immunotherapy was 5.5 months. All 19 patients stopped immunotherapy early due to immune-related adverse effects.

In 4 patients, disease progression occurred immediately after the treatment was stopped, while 8 patients (42%) had a durable response and remained off any additional therapy for at least 6 months from the time of treatment discontinuation. While these findings are noteworthy and compelling, the study population was quite small. It would be interesting to study predictors of such a durable response to immunotherapy. Meanwhile, the researchers are developing a prospective clinical trial that will further explore the outcome of immunotherapy treatment discontinuation in patients without disease progression.

This study provides welcome news for patients who are unable to continue immunotherapy as a result of adverse effects. It is reassuring to see that some patients may continue to benefit from immunotherapy even if they need to discontinue it. More broadly, these findings call into question the current standard of continuous treatment with immunotherapy, though longer-term follow-up of patients is needed to identify patients in whom continuous dosing is not required, and evaluate long-term outcomes in this population.

■ Combining pembrolizumab and low-dose ipilimumab: the KEYNOTE-029 Study. (Abstract 510)

The anti-CTLA-4 antibody ipilimumab and anti-PD-1 antibody pembrolizumab have demonstrated efficacy in a range of patients with advanced malignancies. While these immune checkpoint inhibitors have shown activity as monotherapy, combination therapy has the potential to further improve outcomes. KEYNOTE-029 (NCT02089685) is a phase 1/2 study designed to assess the safety and efficacy of this combination or pegylated interferon alfa-2b (IFN-a) in patients with advanced melanoma or RCC.

The authors have reported on the phase 1 portion of the study in patients with mRCC treated with pembrolizumab + ipilimumab. The study group included patients ≥18 years with advanced/unresectable or metastatic clear cell RCC who received at least one prior therapy for metastatic disease, had at least 1 measurable lesion per RECIST v1.1, and were ECOG PS 0-1. Patients received pembrolizumab 2 mg/kg q3w + low-dose ipilimumab (1 mg/kg q3w for 4 doses) until disease progression, unacceptable toxicity, investigator/patient decision, or 2 years of pembrolizumab treatment. AEs were monitored throughout treatment and for 30 days thereafter and graded per NCI CTCAE v4.0. Primary endpoint was safety; primary efficacy endpoint was ORR assessed per RECIST v1.1 by independent central review. At the time of presentation, 10 patients with RCC had received pembrolizumab + low-dose ipilimumab.

With a median follow-up of 17.4 months (0.9-23.5 months), 70% of patients experienced AEs of any grade, most commonly fatigue (30%); and 50% experienced grade 3-4 AEs, most commonly increased lipase (20%). 50% discontinued pembrolizumab because of AEs, most commonly increased lipase (40%). There were no treatment-related deaths. ORR was 20% (2 partial responses). An additional 3 patients had stable disease and the disease control rate was 50%. From this phase 1 study, Choueiri et al concluded that the combination of pembrolizumab + low-dose ipilimumab for 4 doses, followed by pembrolizumab monotherapy, demonstrates a manageable toxicity profile and preliminary antitumor activity in patients with advanced RCC. Clinical trial information: NCT02089685

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A Very Brief 'Take Home': Summaries of Additional Selected Abstracts from ASCO GU Cover a Broad Spectrum of New Findings

(Editor's note: To access the full abstracts to these abbreviated summaries, please see the link cited in the beginning of this article.)

• Comparative effectiveness of tumor response assessment methods: Standard-of-care versus computer-assisted response evaluation. (Abstract 432)
Brian C. Allen, et al. Duke University Medical Center, Durham, NC
Background: In clinical trials and clinical practice, tumor response assessment with computed tomography (CT) de-

fines critical end points in patients with metastatic disease treated with systemic agents. Methods to reduce errors and improve efficiency in tumor response assessment could improve patient care.
Conclusion: Computer-assisted tumor response evaluation reduced errors and time of evaluation, indicating better overall effectiveness than manual tumor response evaluation methods that are the current standard-of-care.

• **Cryoablation of cT1 renal masses in the "healthy" patient: Early outcomes from Mayo Clinic. (Abstract 433). Harras B. Zaid, et al, Mayo Clinic, Rochester, MN**
Background: Current guidelines suggest that percutaneous thermal ablation (PTA) can be utilized in patients with significant comorbidity who are unable to tolerate surgery (radical or partial nephrectomy). However, the use of PTA in healthy patients, who are otherwise candidates for surgery, has been limited. A single-institutional experience was reviewed in healthy patients electing to undergo cryoablation.
Conclusion: In this cohort of "healthier" patients with cT1 solitary renal masses, cryoablation offered reasonable short-term oncologic control. While longer follow-up data are needed to evaluate for durability of effectiveness, cryoablation in healthy patients, particularly those with challenging surgical anatomy, warrants further study and longer follow-up.

• **Changes in tumor burden and IMDC class after active surveillance (AS) for metastatic renal cell carcinoma (mRCC). (Abstract 435) Davide Bimbatti, et al, Medical Oncology, Azienda Ospedaliera Universitaria Integrata, University of Verona, Verona, Italy**
Background: Targeted therapies (TT) have improved survival in mRCC but treatment-related toxicities may worsen quality of life and lead to treatment discontinuation. AS is a feasible strategy in patients with indolent disease but effects on tumor burden (TB) and prognosis have not been investigated.
Conclusion: AS is an option for management of mRCC pts with good and intermediate prognosis. AS allows for delay in the start of TT, temporarily avoiding toxicity and worsening quality of life. Despite the fact patients on AS have increased TB but rarely a worsening of prognostic class, survival remains acceptable, and the effectiveness of subsequent therapy appears not to be affected.

• **A single-arm biomarker-based phase II trial of savolitinib in patients with advanced papillary renal cell cancer (PRCC). (Abstract 436)Toni K. Choueiri, et al, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA**
Background: Savolitinib (HMPL504/Volitinib, AZD6094) is a potent, selective MET inhibitor. MET and its ligand, HGF, are known to play an important role in the molecular events underlying oncogenesis in PRCC, a disease without a clear effective standard of care and marked by alterations of MET in many patients. This study evaluated savolitinib in PRCC patients dosed at 600 mg daily until disease progression.
Conclusion: In this largest biomarker-profiled trial dedicated to PRCC, savolitinib was generally well tolerated with anti-tumor activity in MET-driven patients. These findings warrant further clinical investigation of savolitinib in MET-driven PRCC.

• **Impact of obesity and adiponectin signaling in patients with renal cell carcinoma: A potential mechanism for the obesity paradox. (Abstract 449) Shintaro Narita, et al, Department of Urology, Akita University Graduate School of Medicine, Akita, Japan**
Background: Obesity increases the risk of renal cell carcinoma (RCC); however, obese patients experience longer survival than non-obese patients. The mechanism of this "obesity paradox" is unknown. This paper examined the impact of obesity, total adiponectin (AD) level, and intratumoral AD receptors expression on RCC aggressiveness and survival, and also investigated the mechanism underlying enhanced cancer aggressiveness in RCC cells with exogenous adiponectin stimulation.
Conclusion: Low BMI and high AD level are associated with cancer aggressiveness and poor survival in RCC patients treated surgically. AD modulates proliferation and apoptosis, which may underlie the "obesity paradox" of RCC.

• **Combined inhibition of autophagy with mTOR inhibitor to enhance cell death in renal cell carcinoma. (Abstract 450) Hua Chen, et al, University of Alberta, Edmonton, AB, Canada**
Background: mTOR (mammalian target of rapamycin) and autophagy are increasingly recognized as being a central cellular and pathological process for numerous human diseases, including renal cell carcinoma (RCC). Depending on the cellular context, autophagy may promote cancer cell survival or cell death. However, little is known about the mechanisms of regulating mTOR activity and autophagic function in RCC. The authors hypothesized that autophagy promotes cell survival via mTOR mediated-phosphatidylinositol 3-kinase (PI3K)/AKT pathway and is regulated by the von Hippel-Lindau (*VHL*) tumor suppressor.
Conclusion: These results support *mTOR* and autophagy as potential targets of anticancer drugs and implicate *VHL* in the control of the autophagy in RCC. Furthermore, this work suggests that combined inhibition of autophagy and mTOR pathways could be a novel therapeutic strategy for the treatment of RCC.

• **Effect of NKTR-214 on the number and activity of CD8+ tumor infiltrating lymphocytes in patients with advanced renal cell carcinoma. (Abstract 454) Michael E. Hurwitz, Yale School of Medicine, New Haven, CT**

Background: Patients with low baseline CD8+ T-cells within the tumor microenvironment (TILs) have a poor response to immune checkpoint inhibitors. Agents designed to specifically activate and expand CD8+ T cells may improve clinical outcomes in patients with low TILs. NKTR-214 is a CD-122-based agonist designed to provide sustained signaling through the heterodimeric IL-2 receptor pathway (IL-2Rb) and preferentially activate and expand NK and effector CD8+ T cells over CD4+ T regulatory cells. A dose escalation, open-label, trial was initiated to assess the safety of NKTR-214 and explore immune changes in the blood and tumor microenvironment in patients with advanced solid tumors.

Conclusion: NKTR-214 increased immune infiltration in the tumor and increased anti-tumor activity in patients who previously progressed on TKIs, with a favorable safety profile. The ability to alter the immune environment and increase PD-1 expression on effectors T cells may improve the effectiveness of anti-PD-1 blockade. A trial combining NKTR-214 and nivolumab is underway.

• **Meta-analysis of disease free survival (DFS) as a surrogate for overallsurvival (OS) in localized renal cell carcinoma (RCC). (Abstract 459) Lauren C. Harshman, et al, Dana-Farber Cancer Institute, Boston, MA**

Background: OS is a critical endpoint for adjuvant RCC trials testing the benefit of early systemic therapy to increase cure rates, but requires long follow-up duration and significant resources. The potential use of DFS as a surrogate for OS when assessing the efficacy of adjuvant therapy in localized RCC was explored.

Conclusion: Across trials of adjuvant systemic therapy for localized RCC, this meta-analysis observed a moderate correlation between 5-year DFS and OS rates and between treatment effects (HRs) on these endpoints. Future meta-analyses of more mature trials in the era of modern adjuvant targeted therapy are needed to further evaluate the surrogacy of intermediate endpoints.

Further granularity may be achieved using individual patient data instead of aggregate data to assess different and earlier time points for surrogacy than are commonly reported.

• **T cell infiltration in matched renal biopsy (bx) and nephrectomy (nx) samples in renal cell carcinoma (RCC). (Abstract 472) Haris Zahoor, et al, Cleveland Clinic, Cleveland, OH**

Background: T-cell infiltration in tumors has been investigated as a biomarker of response to checkpoint inhibitors. There are no data regarding the association of T-cell infiltration in matched biopsy and nephrectomy samples without intervening treatment. Understanding this association could enable further study of this potential biomarker in future neoadjuvant studies. Matched biopsy and nephrectomy samples (without intervening systemic therapy) were ident- fied from patients with non-metastatic RCC.

Conclusion: The analysis found a modest correlation between the frequencies of CD8+ T cells between matched biopsy and nephrectomy samples (r= 0.39; p=0.03). CD3+ and CD4+T cells did not show significant correlation. The authors concluded that biopsy material could be potentially used to accurately assess the degree of CD8+T cell infiltration in RCC.

• **Cabozantinib for the treatment of patients with metastatic varianthistology renal cell carcinoma (vhRCC): A retrospective study. (Abstract 478) Matthew T. Campbell, et al, The University of Texas MD Anderson Cancer Center, Houston, TX**

Background: Cabozantinib (C) prolongs overall survival (OS) and progression-free survival (PFS) in patients with metastatic clear-cell renal cell carcinoma (ccRCC) that progressed on first-line VEGFR-TKI. No standard of care systemic therapy exists for the management of patients with metastatic vhRCC.

Conclusion: In this retrospective study, cabozantinib produced a clinically meaningful benefit in patients with metastatic variant histology RCC, the majority of whom had progressive disease on prior VEGFR-TKIs. Prospective trials of cabozantinib in vhRCC are warranted.

• **Clinical activity of PD1/PDL1 inhibitors in metastatic non-clear cell renal cell carcinoma (nccRCC). (Abstract 482) Raphael Brandao Moreira, et al, Dana-Farber Cancer Institute, Boston, MA**

Background: PD1/PDL1 inhibitors have shown significant activity in the treatment of patients with metastatic clear cell renal cell carcinoma (ccRCC), but their activity in nccRCC is poorly characterized.

Conclusion: PD1/PDL1 blockade resulted in some activity in patients with various nccRCC histologies. However, prior to routine use of PD-1/PD-L1 blocking agents in nccRCC, prospective trials are necessary.

• **Tumor genomic analysis for 128 renal cell carcinoma (RCC) patients receiving first-line everolimus: (Abstract 484) Correlation between outcome and mutations status in MTOR, TSC1, and TSC2. Martin Voss, et al, Memorial Sloan Kettering Cancer Center, New York, NY**

Background: mTOR inhibitors are approved for the management of metastatic RCC. Prior studies have suggested that somatic mutations in mTOR, TSC1, and TSC2 may sensitize tumors to everolimus. This hypothesis was tested through next generation sequencing (NGS) of tumors from a large cohort of patients treated with everolimus in the randomized RECORD3 trial of first-line everolimus vs. sunitinib.

Conclusion: "One-dimensional" mutation status for core components of the mTOR signaling pathway did not cor-

relate with PFS in this dataset. Grouping based on more detailed characterization incorporating copy number status and functional annotation may provide better insights and should be considered for future biomarker development.

• **Impact of cytoreductive nephrectomy on timing of systemic therapy in metastatic kidney cancer. (Abstract 503) Liam Connor Macleod, et al, University of Washington, Seattle, WA**
Background: High rates of disease control with systemic therapy in the post-cytokine era for metastatic renal cell carcinoma (mRCC) cause apprehension that cytoreductive nephrectomy (CN) may delay effective systemic therapy. This study evaluated factors associated with early mortality and time to systemic therapy after CN.
Conclusion: These data suggest that markers of frailty, progressive disease, and surgical morbidity may contribute to surgical-related deaths or hinder patients receiving potentially disease-controlling therapy when treated with initial CN in mRCC. Going forward, existing surgical prognostic models could incorporate risk factors for surgical-related morbidity/mortality and risk factors for delay in initiating postoperative systemic therapy when considering CN.

• **A phase 1 study of alpha-1,3-galactosyltransferase-expressing allogeneic renal cell carcinoma immunotherapy in patients with metastatic renal cell cancer. Hans J. Hammers, et al, The University of Texas Southwestern Medical Center, Dallas, TX**
Background: HyperAcute Renal (HAR) immunotherapy consists of two allogeneic renal cancer cell lines that have been genetically modified to express the carbohydrate a(1,3)Gal, to which humans have an inherent pre-existing immunity. HAR is designed to leverage this mechanism to educate the immune system towards antigens expressed by the patient's own tumor cells.
Conclusion: RCC is considered an immunogenic tumor based on its response rate to immune checkpoint blockade and IL-2, occasional spontaneous regression, and the high level of tumor T cell infiltration. HAR was well tolerated in this patient population. Therefore, RCC is an appropriate tumor type to target with combination immunotherapy including HAR. KCJ

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and a new Japanese study. So the answer is true. The mechanism of this "obesity paradox" is unknown. The Japanese paper examined the impact of obesity, total adiponectin (AD) level, and intratumoral AD receptors expression on RCC aggressiveness and survival, and also investigated the mechanism underlying enhanced cancer aggressiveness in RCC cells with exogenous adiponectin stimulation.

Some findings tend to be counterintuitive and challenge the conventional wisdom. The value of medical symposia, perhaps, is that we are able to find an abundance of them in one place, such as the recent GU ASCO meeting in Orlando. However, counterintuitive findings take root with difficulty as illustrated in Michael Lewis' The Undoing Project based on the Nobel-prize winning research of Kahneman and Tversky.

Returning to our original question: do new medical meetings, version 2.0, so to speak, move the needle in kidney cancer and have an impact on our practices?

Like cloud-based technology, health care doesn't really have a true "2.0." New knowledge incrementally accumulates and changes practice patterns. Some of this new knowledge comes from medical meetings. It accumulates slowly, just as the acceptance of evidence-based medicine as a paradigm took decades to take root. In an industry where change can bring harm to a vulnerable population, it is no secret that clinics and hospitals always seek to improve care. The part that is less emphasized and perhaps underappreciated, however, is the importance that we improve care in increments. And where do the increments come from, at least to some extent? Medical meetings are just one source, and hopefully, they help us "move the needle" toward improved quality of care.

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Renal Cell Carcinoma With Pulmonary Metastasis and Metachronous Non-Small Cell Lung Cancer. Bowman IA, Pedrosa I, Kapur P, et al. *Clin Genitorurin Cancer*. 2017 Feb 6. pii: S1558-7673(17)30042-3. doi: 10.1016/j.clgc. 2017.01.026.

Summary: The development of a second primary malignancy in a patient with a preexisting diagnosis of metastatic cancer may be easily overlooked or misattributed to progression of disease. This report includes 3 patients with clear-cell renal cell carcinoma (RCC) metastatic to the lungs who were subsequently diagnosed with non-small-cell lung cancer (NSCLC). The authors examined the frequency of this occurrence within their institution and report on the radiographic findings that may help distinguish between metastatic RCC and primary lung cancers. Patients who received systemic targeted therapy for metastatic RCC between January 2006 and October 2013 were identified, and the proportion and incidence rate for developing NSCLC with preexisting metastatic RCC were calculated.

Conclusion: The subsequent diagnosis of a primary lung cancer in metastatic RCC patients occurred in 2% of patients and is underreported in the literature. Primary NSCLC may be underdiagnosed in patients with metastatic RCC. Both the radiographic appearance and clinical behavior of a lesion may hold clues that can help distinguish between a new primary and progression of metastatic disease.

Outcome of Patients with Renal Cell Carcinoma and Multiple Glandular Metastases Treated with Targeted Agents. Grassi P, Doucet L, Giglione P, et al. *Oncology*. 2017 Feb 17. doi: 10.1159/000455970

Summary: This study evaluated the outcome of RCC patients with multiple glandular metastases (MGM) treated with targeted therapies (TTs). Sixty-four MGM patients treated between 1993 and 2014 were retrospectively identified from a database of 274 RCC patients with pancreatic metastases (PM) from 11 European centers. The survival of MGM patients was compared with that of both patients with PM only and a cohort of 325 RCC patients with non-GM (control group) treated with TTs. Survival was estimated using the Kaplan-Meier method and was statistically compared using the log-rank test. Fifty-six patients (88%) had at least 2 MGM, 7 patients (11%) had 3 MGM and 1 patient had 4 MGM, while non-GM were present in the remaining patients. The median overall survival (OS) was 54.2 months for MGM and 73.4 months for patients with PM only. The median OS in the control group was 22.7 months and statistically inferior to both MGM ($P < 0.001$) and PM patients ($P < 0.001$).

Conclusion: MGM from RCC are associated with a remarkable survival. Despite some limitations, these findings suggest that GM might be considered a predictor of a favorable prognosis.

Transarterial Yttrium-90 Radioembolization Treatment of Patients with Liver-Dominant Metastatic Renal Cell Carcinoma. Kis B, Shah J, Choi J, et al. *J Vasc Interv Radiol*. 2017 Feb;28(2):254-259. doi: 10.1016/j.jvir. 2016.09.025.

Summary: From July 2010 to December 2014, 18 patients with liver-dominant metastatic RCC were treated with yttrium-90 glass microsphere radioembolization. Retrospective review of medical records and imaging studies was performed to evaluate toxicities, treatment response, and overall survival. The median follow-up period from radioembolization treatment was 17.8 months. Median overall survival from RCC diagnosis was 64 months, from diagnosis of liver metastasis was 29 months, and from radioembolization treatment was 22.8 months. After treatment, 10 patients reported grade 1 clinical toxicities, and 8 patients had grade 1 or 2 biochemical toxicities. The best radiographic responses of 17 patients who underwent contrast-enhanced cross-sectional imaging showed complete response in 16 patients and partial response in 1 patient evaluated by modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria. The last available imaging of these 17 patients demonstrated complete response in 14 patients, partial response in 1 patient, and progression of disease in 2 patients. Images of a patient who underwent noncontrast CT showed stable disease as best response and stable disease on the last available imaging evaluated by RECIST.

Conclusion: Radioembolization is safe and effective and led to improved hepatic disease control and overall survival in patients with liver-dominant metastatic RCC.

Axitinib Versus Sorafenib in First-Line Metastatic Renal Cell Carcinoma: Overall Survival From a Randomized Phase III Trial. Hutson TE, Al-Shukri S, Stus VP, et al. *Clin Genitourin Cancer*. 2017 Feb; 15(1):72-76. doi: 10.1016/j.clgc.2016.05.008.

Summary: In a randomized phase 3 trial in treatment-naive patients with metastatic renal cell carcinoma (RCC), axitinib vs sorafenib yielded numerically longer progression-free survival (median, 10.1 vs. 6.5 months; $P = .038$) and significantly higher objective response rate (32% vs. 15%; $P = .0006$). This report updates results. Previously untreated patients with metastatic RCC (n = 288), stratified according to Eastern Cooperative Oncology Group performance status (ECOG PS; 0 vs. 1), were randomized 2:1 to receive axitinib 5 mg twice per day (b.i.d.; n = 192) or sorafenib 400 mg b.i.d. (n = 96). Median OS was 21.7 months (18.0-31.7) with axitinib versus 23.3 months (18.1-33.2) with sorafenib. Among patients with ECOG PS of 0, median OS was numerically longer with axitinib than with sorafenib (41.2 vs. 31.9 months; whereas among patients with ECOG PS 1, median OS was shorter with axitinib than with sorafenib (14.2 vs. 19.8 months; HR, 1.203; 1-sided; $P = .7973$). Incidence and severity of common adverse events were consistent with previous reports.

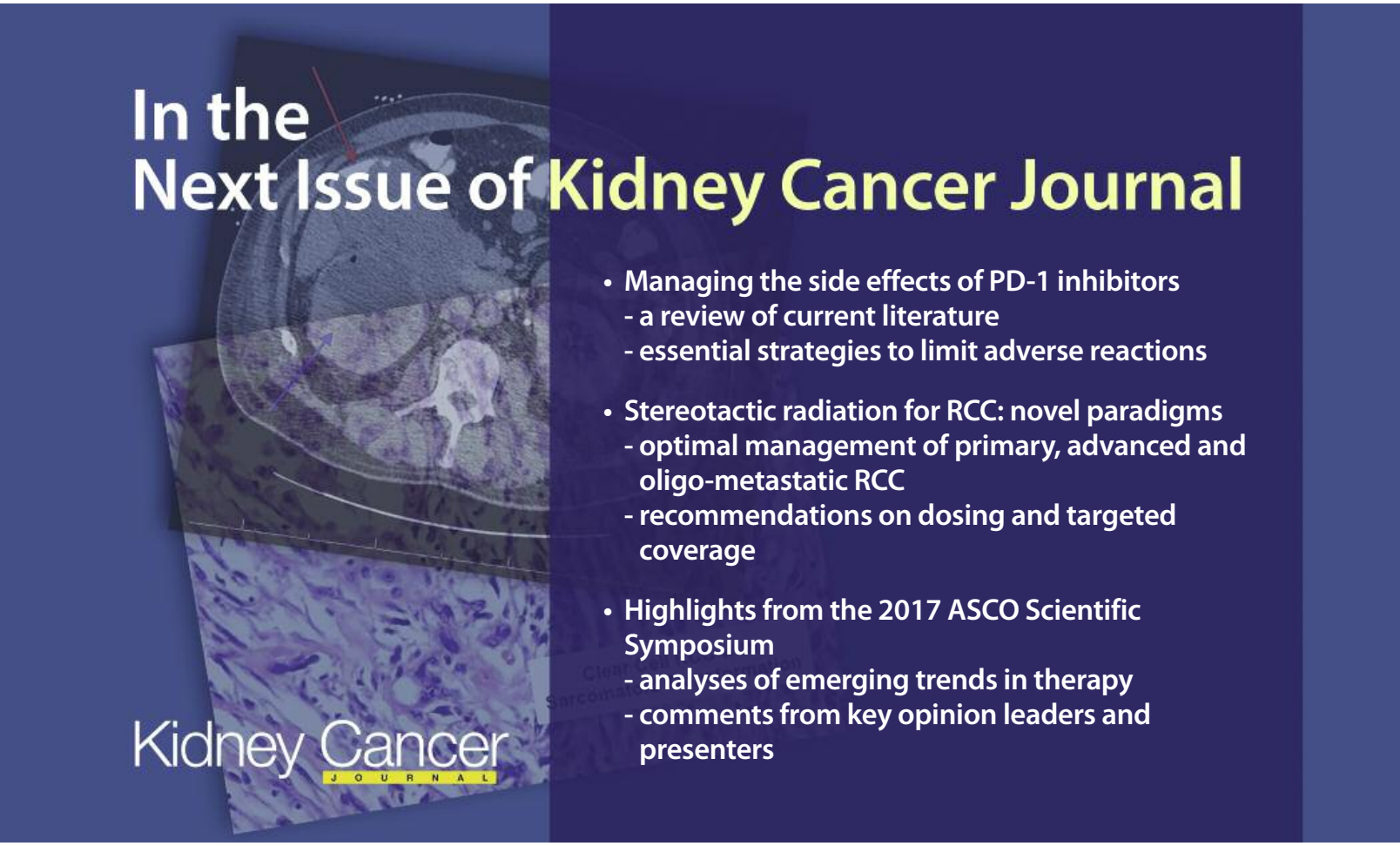
Conclusion: OS was similar between axitinib and

sorafenib in treatment-naive patients with metastatic RCC, and no new safety signals emerged.

Inhibiting Histone Deacetylase as Means to Reverse Resistance to Angiogenesis Inhibitors: Phase I Study of Abexinostat Plus Pazopanib in Advanced Solid Tumor Malignancies. **Aggarwal R, Thomas S, Pawlowska N, et al. *J Clin Oncol*. 2017 Feb 21:JCO2016705350. doi: 10.1200/JCO.2016.70.5350.**

Summary: This phase 1 trial evaluated epigenetic modulation of vascular endothelial growth factor (VEGF) and hypoxia-inducible factor by using a histone deacetylase abexinostat in combination with pazopanib to enhance response and reverse resistance. Pazopanib was administered once a day on days 1 to 28 and abexinostat was administered orally twice a day on days 1 to 5, 8 to 12, and 15 to 19 (schedule A) or on days 1 to 4, 8 to 11, and 15 to 18 (schedule B). Dose escalation (3 + 3 design) in all solid tumors was followed by dose expansion in renal cell carcinoma (RCC). Fifty-one patients with RCC were enrolled, including 30 (59%) with one or more lines of prior VEGF-targeting therapy. Five dose-limiting toxicities, including fatigue (n = 2), thrombocytopenia (n = 2), and elevated AST/ALT (n = 1), were observed with schedule A; one dose-limiting toxicity was observed (elevated AST/ALT) was observed with schedule B. Grade ³ 3 related adverse events included fatigue (16%), thrombocytopenia (16%), and neutropenia (10%). The recommended phase 2 dose was established as abexinostat 45 mg/m2 twice a day administered per schedule B plus pazopanib 800 mg/d. Objective response rate was 21% overall and 27% in the RCC subset. Median duration of response was 9.1 months (1.2 to > 49 months). Eight patients (16%) had durable control of disease for > 12 months. Durable tumor regressions were observed in seven (70%) of 10 patients with pazopanibrefractory disease, including one patients with RCC with ongoing response > 3.5 years. Peripheral blood histone acetylation and HDAC2 gene expression were associated with durable response to treatment.

Conclusion: Abexinostat is well tolerated in combination with pazopanib, allowing prolonged exposure and promising durable responses in pazopanib- and other VEGF inhibitor-refractory tumors, which supports epigenetically mediated reversal of treatment resistance. KCJ



(continued from page 9)

officer of AVEO. "We believe tivozanib offers a unique opportunity to potentially overcome this barrier, and look forward to initial results from the Phase 1 portion of the TiNivo trial in the first half of 2017."

Discontinuation Recommended of ADAPT Phase 3 Trial of Rocapuldencel-T in Metastatic RCC After Interim Data Review

DURHAM, NC—Feb. 22, 2017, Argos Therapeutics Inc. has announced that the Independent Data Monitoring Committee (IDMC) for the company's pivotal Phase 3 ADAPT clinical trial of rocapuldencel-T in combination with sunitinib/standard-of-care for the treatment of metastatic renal cell carcinoma (mRCC) has recommended that the study be discontinued for futility based on its planned interim data analysis. The IDMC concluded that the study was unlikely to demonstrate a statistically significant improvement in overall survival in the combination treatment arm, utilizing the intent-to-treat population, the primary endpoint of the study. The IDMC noted that rocapuldencel-T was generally well-tolerated in the trial.

Rocapuldencel-T is an individualized immunotherapy designed to capture mutated and variant antigens specific to each patient's tumor and induce an immune response targeting that patient's tumor antigens. The randomized Phase 3 ADAPT trial evaluating rocapuldencel-T plus sunitinib/standard-of-care therapy versus standard-of-care therapy completed enrollment in July 2015. A total of 462 mRCC patients were randomized to the trial. The primary endpoint of the trial is a statistically significant improvement in overall survival.

CB-839 Drug Promising for Clear Cell, Papillary RCC

MUNICH — An experimental drug, CB-839, shows promise in treating kidney cancer, according to research presented at an international oncology conference in Munich. The conference is sponsored by the American Association for Cancer Research, the European Organisation for Research and Treatment of Cancer (EORTC), and the US National Cancer Institute. CB-839 targets glutaminase, an enzyme involved in the conversion of glutamine to glutamate, a nutrient that cancer cells need to survive, the researchers explained. This Phase 1 clinical trial found that the drug was effective in most patients with advanced kidney cancer when used in combination with everolimus.

In the 15 patients in the study, the dual treatment controlled tumors in 93% of the patients, who had either clear cell or papillary renal cell cancer. Tumors shrank by more than 30 percent in one patient, were stable in 13 patients, and grew by more than 20% in one patient. All 12 patients with clear cell kidney cancer had their disease controlled. The researchers found the drug to be well tolerated.

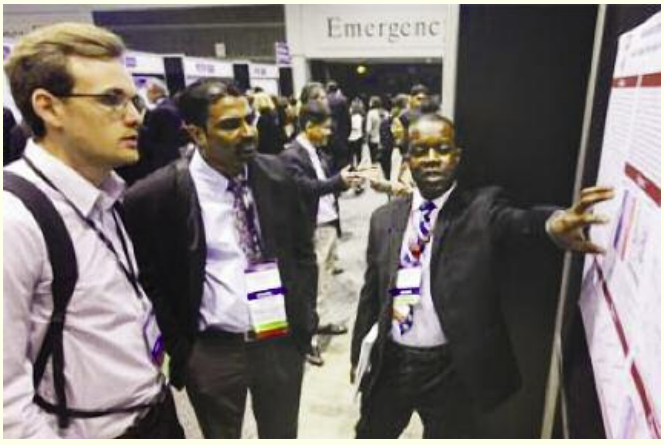
"Glutaminase is a very interesting target and previous work in the lab has shown that CB-839 is effective at inhibiting it in renal cell cancers and that it enhances the anti-tumor efficacy of everolimus," study author Funda Meric-Bernstam, MD, chair of the department of investigational cancer therapeutics at the University of Texas MD Anderson Cancer Center in Houston, said in an EORTC news release. "To date, tumors in 93% of patients with clear cell and papillary renal cell cancers have had tumor control from the regimen, with a median time without their cancer growing of 8.5 months."

Twelfth European International Kidney Cancer Symposium to Be Held in Munich

MUNICH—Bringing together key individuals and representatives from leading laboratories and centers working with renal cell carcinoma, the Twelfth European International Kidney Cancer Symposium seeks to provide a forum for the exchange of ideas and information that will continue to frame directions for future research and treatment. The symposium will be held at the Westin Grand Munich, April 21-22. To register, visit the Kidney Cancer Association website at https://www.starwoodmeeting.com/Book/kidney2017

ASCO Scientific Sessions Scheduled for June

CHICAGO—The 2017 Scientific Sessions of the American Society of Clinical Oncology will be held in Chicago, June 2-6.



The annual meeting brings together more than 30,000 oncology professionals from around the world to discuss state-of-the-art treatment modalities, new therapies, and ongoing controversies in the field. KCJ

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