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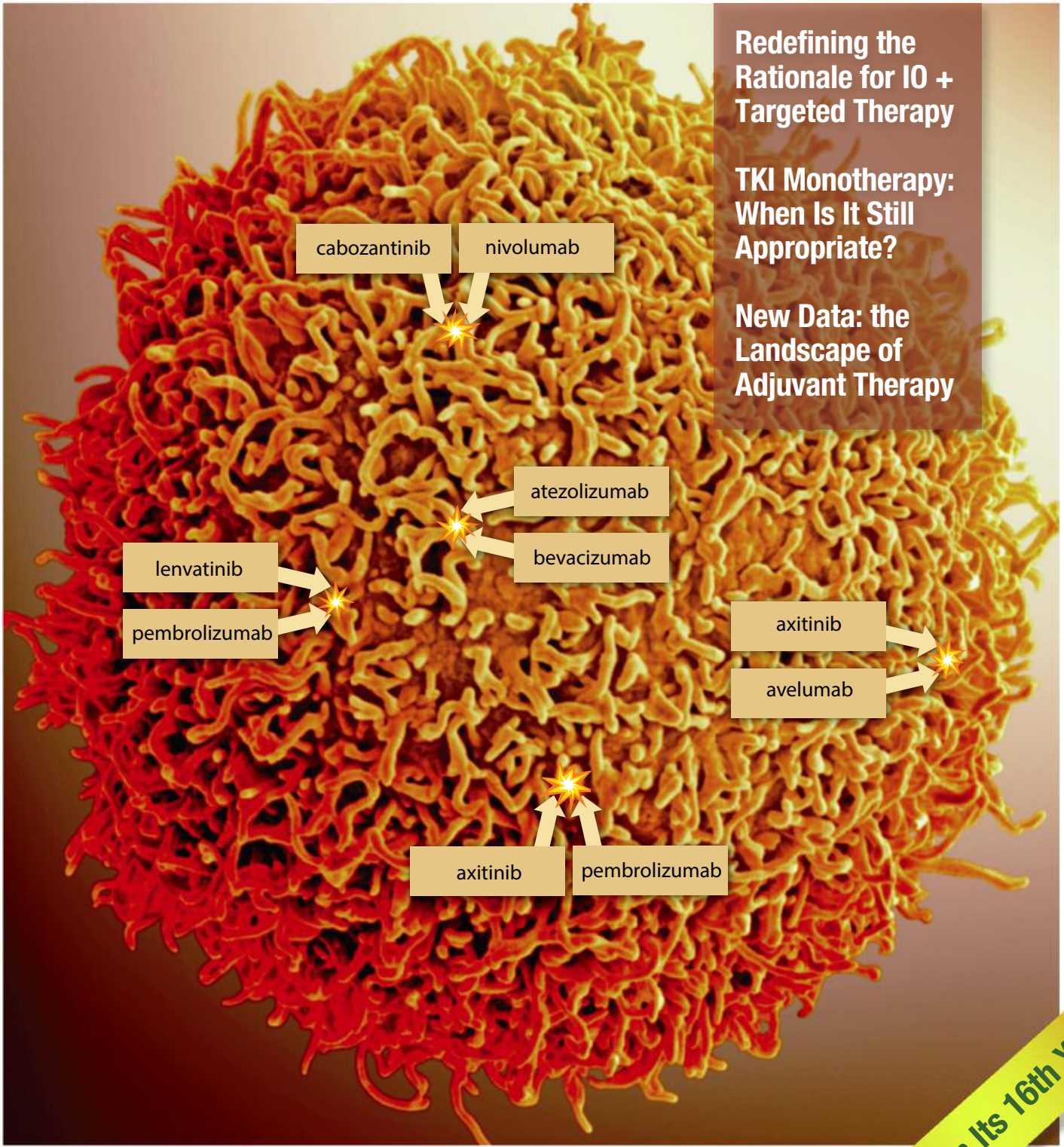

Redefining the Rationale for IO + Targeted Therapy

TKI Monotherapy: When Is It Still Appropriate?

New Data: the Landscape of Adjuvant Therapy

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

Now in Its 16th Year

After failure of a prior systemic advanced RCC therapy,

MAKE THE NEXT MOVE TO INLYTA® (axitinib)

Demonstrated efficacy • Safety and tolerability profile

EFFICACY MEASURES

From the AXIS trial: an open-label, phase 3 trial in metastatic RCC after failure of one prior systemic therapy (N=723)*

PROGRESSION-FREE SURVIVAL (PFS): PRIMARY ENDPOINT

6.7 months median PFS vs 4.7 months with sorafenib

(95% CI: 6.3, 8.6 and 4.6, 5.6, respectively; HR=0.67 [95% CI: 0.54, 0.81; *P*<.0001])

OBJECTIVE RESPONSE RATE (ORR): SECONDARY ENDPOINT

19.4% ORR vs 9.4% with sorafenib

(95% CI: 15.4, 23.9 and 6.6, 12.9, respectively; risk ratio: 2.06 [95% CI: 1.4, 3.0])

- The *P* value for the risk ratio is not included because it was not adjusted for multiple testing
- All responses were partial responses per RECIST criteria[1]

OVERALL SURVIVAL (OS): SECONDARY ENDPOINT

20.1 months median OS vs 19.2 months with sorafenib

(95% CI: 16.7, 23.4 and 17.5, 22.3, respectively; HR=0.97 [95% CI: 0.80, 1.17; the difference between the treatment arms was not statistically significant])

*From AXIS, a multicenter, open-label, phase 3 trial of 723 patients with metastatic RCC 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 ORR, OS, and safety and tolerability.[1,2]

AEs=adverse events; RCC=renal cell carcinoma; RECIST=Response Evaluation Criteria in Solid Tumors.

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.

TOLERABILITY CONSIDERATIONS

In the phase 3 AXIS trial*

91% of patients did not discontinue INLYTA due to AEs

- 9% of patients discontinued INLYTA (n=34/359) due to AEs vs 13% of patients with sorafenib (n=46/355)
  - —Overall, 61% of patients receiving INLYTA discontinued treatment vs 71% receiving sorafenib[1]
  - —In both study groups, the most common reasons for discontinuation included disease progression or relapse and AEs[1]
- Fewer patients receiving INLYTA had dose modifications or temporary delay of treatment due to AEs compared with patients receiving sorafenib (55% vs 62%, respectively)

MOST COMMON AEs

- 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%).

Reversible Posterior Leukoencephalopathy Syndrome (RPLS) has been observed. If signs or symptoms occur, permanently discontinue treatment.

Monitor for **proteinuria** before initiation of, and periodically throughout, treatment. For moderate to severe proteinuria, reduce the dose or temporarily interrupt treatment.

Liver enzyme elevation has been observed during treatment with INLYTA. Monitor ALT, AST, and bilirubin before initiation of, and periodically throughout, treatment.

For patients with moderate **hepatic impairment**, the starting dose should be decreased. INLYTA has not been studied in patients with severe hepatic impairment.

Women of childbearing potential should be advised of potential hazard to the fetus and to avoid becoming **pregnant** while receiving INLYTA.

Avoid strong **CYP3A4/5 inhibitors**. If unavoidable, reduce the dose. Grapefruit or grapefruit juice may also increase INLYTA plasma concentrations and should be avoided.

Avoid strong **CYP3A4/5 inducers** and, if possible, avoid moderate CYP3A4/5 inducers.

References: 1. Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. *Lancet.* 2011; 378(9807):1931-1939. **2.** Data on file. Pfizer Inc, New York, NY.

Please see Brief Summary of full Prescribing Information on the following pages.

Printed in USA/February 2018

Pfizer U.S. Pharmaceuticals

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

About the Cover
Simulation suggests effect of combined immunotherapy and targeted therapy on a colored scanning electron micrograph of a kidney cancer cell. A broad spectrum of these combination therapies, as depicted in the image, are undergoing study as part of a synergistic strategy to address various pathways of renal cell carcinoma. (Copyright, Photo Science Library)

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KCJ GUEST EDITOR'S MEMO

Predictive Biomarkers in Kidney Cancer- The Last Crusade or the Temple of Doom?


Brian M. Shuch, MD

My mission as Guest Editor for this issue of the *Kidney Cancer Journal* has a twofold purpose. The first is to alert readers to the upcoming 17th International Kidney Cancer Symposium (IKCS) in Miami, November 2-3- a fantastic scientific program highlighting some of the outstanding progress in conquering kidney cancer this year and the exciting work expected in 2019. In my welcoming remarks at this year's scientific sessions, sponsored by the Kidney Cancer Association, I will highlight an exciting agenda with arguably the broadest spectrum of topics related to renal cell carcinoma at any oncology symposium this year. The second message in this Guest Editor's Memo is to mention how one of our topics covered in this issue touches upon a segment of the program at the IKCS—biomarkers.

Biomarkers continue to evolve in RCC; from protein markers to genomic alterations and even recently, the stool microbiome. One of the planned sessions at the IKCS meeting involves where we stand for prognostic and predictive biomarkers including a discussion of the past, the present, and the future. As the headline above suggests, the search for a reliable and predictive biomarker has been exhaustive over the last decade and feels more like a plot line to an Indiana Jones movie. How many meetings have you attended where abstracts have proposed new exciting biomarkers yet validation studies became trapped and failed to meet their promise or the investigators strayed from their path and didn't pursue clinical utility studies? Nonetheless, there are positive signs that the "Quest for the Holy Grail" is beginning to move a bit closer to the goal of identifying biomarkers to select therapy in view of a whole host of clinical studies pursuing testable hypotheses.

The ultimate goal of a candidate biomarker is demonstration of validity as an integral or integrated biomarker in the clinical trial setting. Several biomarker driven trials are currently open in phase III trials evaluating non-clear cell RCC using alterations in the MET pathway as either integral or integrated biomarkers. SAVOIR explores the role of potent MET inhibitor savolitinib vs sunitib in papillary RCC. In this trial, MET alterations (mutation or MET/HGF amplication) serve as an integral biomarker dictating trial eligibility. PAPMET (SWOG S1500) is looking at various MET inhibitors in all papillary RCC. In this trial, MET alterations and papillary subtype (1, 2, or unclassified) by central path review are used as integrated biomarkers with the hypothesis these influence progression-free survival and response. These protocols build upon prior work from the CREATE trial with crizotinib and a phase II trial of savolitinib (NCT02127710). These larger phase III studies will be useful to determine if this biomarker has clinical utility or is a forged relic.

Tumor sequencing is now readily available in house at some institutions or

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Clarifying the Checkpoint Inhibitor Treatment Options in Non-clear Cell RCC

To the Editor:

This spring, we launched a new papillary patient community that now has about 120 members and continues to grow. (For what it's worth, we also have a large chromophobe community and a recently launched unclassified renal cell carcinoma [RCC] community). As a rule, we don't create communities unless we're asked to do so, rather we let existing communities thrive and work within them to share information and provide support where we can.

This week, a caregiver in the papillary community mentioned that she was looking for a clinical trial involving ipi/nivo (ipilimumab/nivolumab) for her husband since "it wasn't approved for pRCC." When I explained to her that it was approved, she shared an article from the *Kidney Cancer Journal* stating clearly that it wasn't**.** [Liu ST, Wong K, Hui G, Kelley K, Pantuck AJ, Drakaki A. The classification and treatment of non-clear cell renal cell carcinoma. *Kidney Cancer Journal*. 2018;16:17-25.]

She was seeking help to get compassionate use. Upon further investigation, I found two other patients in other general RCC communities with the same reference.

My understanding of the label is that ipi/nivo is approved for kidney cancer and that there isn't a designation related to histology. I believe that's also true for nivolumab as monotherapy (and all other labels in kidney cancer for that matter).

Of course I understand that trials are conducted using predominantly clear cell patients and that navigating options for non-clear cell is difficult. I'm not making a case that every patient will benefit from checkpoint inhibitors - nor are we pushing this in any of the communities. But we're seeing more and more insurance denials these days and it's imperative that any messaging put out doesn't imply that FDA labeling excludes certain patients. Seventy percent of our patients are treated in the community setting. One article is all it takes to set things back and keep doctors from prescribing even in cases where patients might benefit.

Below is what is being shared - along with a link to the longer article.

"In general, the current treatment of choice for non-clear cell RCC is a vascular endothelial growth factor (VEGF) receptor inhibitor followed by a mammalian target of rapamycin (mTOR) inhibitor at the time of progression. Immunotherapy with checkpoint inhibitors is not yet FDA approved for non-clear cell RCC."

http://kidney-cancer-journal.com/liu_v16n1/

Perhaps the *Kidney Cancer Journal* could provide an update since the article was published prior to combination therapy approval? We could share that within our communities and dispel any concerns that checkpoint inhibitors aren't FDA approved in non-clear-cell RCC.

Any help you can provide is greatly appreciated!

Best,

Dena Battle
President, KCCURE

The authors' response:

We would like to thank Ms. Battle for pointing out the important fact that although there are currently no drugs with specific regulatory approval from the US FDA for non-clear cell RCC, all the targeted and immunotherapies approved in kidney cancer to date, including the recent approval of nivolumab and ipilimumab in combination, have been issued with the marketing indication for "advanced renal cell carcinoma."

These broad approvals, which encompass all sub-types of RCC, were issued regardless of the fact that the clinical studies leading to these approvals were conducted nearly exclusively in patients having clear cell predominant tumors, and often using risk stratification systems such as the one used by the IDMC which were developed nearly exclusively in clear cell patients. However, as we tried to point out in our review, RCC represents not one entity but rather a family of renal cortical tumors that arise in different cells of the kidney, have different underlying genetics and molecular biology, appear differently histologically, and which behave differently clinically.

It is not unreasonable to expect, therefore, that tumors with this many important differences might respond differently to "targeted" agents that have a mechanism of action directed to a specific molecular alteration. We would not advocate treating neuroendocrine and non-small cell carcinomas of the lung, for example, the same way simply because they both arose in the same organ, but rather ideally we would make treatment decisions based on evidence-based clinical data.

While we regret the impression left by our review article that currently patients with non-clear RCC tumors did not have access to approved drugs under the broad regulatory approval framework of the FDA, we would like to reiterate the need that we see for both industry and academia to do better for patients with non-clear histologies, both by developing agents that target the underlying biology of these tumors, and by doing the difficult studies to demonstrate the efficacy and safety of agents specifically in these challenging (since rare) patient populations.

To this end, we greatly anticipate the results of studies such as the now completely accrued BMS 920, which included patients with non-clear cell histology, and which will provide prospective data on the benefits of nivolumab/ipilimumab for non-clear cells tumors. Until then, however, the NCCN guidelines currently list checkpoint blockade as a systemic therapy option for non-clear cell histology, and, in the absence of other data in this treatment setting, it should be considered a reasonable treatment option offered to patients who have metastatic non-clear cell RCC.

Sandy T.Liu, MD
Allan J. Pantuck, MD
Alexandra Drakaki, MD, PhD

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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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.

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

Manuscript Preparation

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

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

References

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

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Seventeenth International Kidney Cancer Symposium

November 2-3, 2018

Doral National Miami Hotel, Miami, Florida

KidneyCancer.org

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For more information about the Kidney Cancer Association and about the Seventeenth International Kidney Cancer Symposium in Miami go to:

www.kidneycancer.org www.kidneycancersymposium.com

Essential Peer-Reviewed Reading in Kidney Cancer

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

Sunitinib alone or after nephrectomy in metastatic renal-cell carcinoma. Méjean A, Ravaud A, Thezenas S, et al. *N Engl J Med.* 2018 Aug 2; doi: 10.1056/NEJMoa 1803675.

Summary: Cytoreductive nephrectomy has been the standard of care in metastatic renal-cell carcinoma for 20 years, supported by randomized trials and large, retrospective studies. However, the efficacy of targeted therapies has challenged this standard. This phase 3 trial randomly assigned, in a 1:1 ratio, patients with confirmed metastatic clear-cell renal-cell carcinoma at presentation who were suitable candidates for nephrectomy to undergo nephrectomy and then receive sunitinib (standard therapy) or to receive sunitinib alone. Randomization was stratified according to prognostic risk (intermediate or poor) in the Memorial Sloan Kettering Cancer Center prognostic model. Patients received sunitinib at a dose of 50 mg daily in cycles of 28 days on and 14 days off every 6 weeks. The primary end point was overall survival. A total of 450 patients were enrolled from September 2009 to September 2017. At interim analysis, the median follow-up was 50.9 months, with 326 deaths observed. The results in the sunitinib-alone group were noninferior to those in the nephrectomy-sunitinib group with regard to overall survival. Median overall survival was 18.4 months in the sunitinib-alone group and 13.9 months in the nephrectomy-sunitinib group. No significant differences in response rate or progression-free survival were observed. Adverse events were as anticipated in each group.

Conclusion: Sunitinib alone was not inferior to nephrectomy followed by sunitinib in patients with metastatic renal-cell carcinoma who were classified as having intermediate-risk or poor-risk disease.

VHL substrate transcription factor ZHX2 as an oncogenic driver in clear cell renal cell carcinoma. Zhang J, Wu T, Simon J, et al. *Science.* 2018 Jul 20;361 (6399):290-295.

Summary: Inactivation of the von Hippel-Lindau (VHL) E3 ubiquitin ligase protein is a hallmark of clear cell renal cell carcinoma (ccRCC). Identifying how pathways affected by VHL loss contribute to ccRCC remains challenging. A genome-wide in vitro expression strategy was used to identify proteins that bind VHL when hydroxylated. Zinc fingers and homeoboxes 2 (ZHX2) was found as a VHL target, and its hydroxylation allowed VHL to regulate its protein stability. Tumor cells from ccRCC patients with VHL loss-of-function mutations usually had increased abundance and nuclear localization of ZHX2.

Conclusion: Functionally, depletion of ZHX2 inhibited VHL-deficient ccRCC cell growth in vitro and in vivo. Mechanistically, integrated chromatin immunoprecipitation sequencing and microarray analysis showed that ZHX2 promoted nuclear factor B activation. These studies reveal ZHX2 as a potential therapeutic target for ccRCC.

Validation of the 16-gene recurrence score in patients with locoregional, high-risk renal cell carcinoma from a phase III trial of adjuvant sunitinib. Rini BI, Escudier B, Martini JF, et al. *Clin Cancer Res.* 2018 Sep 15;24(18): 4407-4415.

Summary: Adjuvant sunitinib prolonged disease-free survival in patients with locoregional high-risk renal cell carcinoma (RCC) in the S-TRAC trial (ClinicalTrials.gov NCT00375674). The 16-gene Recurrence Score (RS) assay was previously developed and validated to estimate risk for disease recurrence in patients with RCC after nephrectomy. This analysis further validated the prognostic value of RS assay in patients from S-TRAC and explored the association of RS results with prediction of sunitinib benefit. The analysis was prospectively designed with prespecified genes, algorithm, endpoints, and analytical methods. Primary RCC was available from 212 patients with informed consent; primary analysis focused on patients with T3 RCC. Gene expression was quantitated by RT-PCR. Time to recurrence (TTR), DFS, and renal cancer-specific survival (RCSS) were analyzed using Cox proportional hazards regression. Baseline characteristics were similar between patients with and those without RS results, and between the sunitinib and placebo arms among patients with RS results. RS results predicted TTR, DFS, and RCSS in both arms, with the strongest results observed in the placebo arm. When high versus low RS groups were compared, HR for recurrence was 9.18 [95% confidence interval (CI), 2.15-39.24) in the placebo arm; interaction of RS results with treatment was not significant.

Conclusion: The strong prognostic performance of the 16-gene RS assay was confirmed in S-TRAC, and the RS assay is now supported by level IB evidence. RS results may help identify patients at high risk for recurrence who may derive higher absolute benefit from adjuvant therapy.

An empirical approach leveraging tumorgrafts to dissect the tumor microenvironment in renal cell carcinoma identifies missing link to prognostic inflammatory factors. Wang T, Lu R, Kapur P, et al. *Cancer Discov.* 2018 Sep;8(9):1142-1155.

Summary: By leveraging tumorgraft (patient-derived

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

JAVELIN Renal 101 Update: Bavencio® (avelumab) plus Inlyta® (axitinib) significantly improved PFS in previously untreated patients with advanced RCC

DARMSTADT, GERMANY—Positive top-line results have been announced from the pivotal Phase III JAVELIN Renal 101 study evaluating bavencio® (avelumab) in combination with inlyta® (axitinib), compared with Sutent® (sunitinib) as initial therapy for patients with advanced renal cell carcinoma (RCC). As part of a planned interim analysis, an independent data monitoring committee confirmed that the trial showed a statistically significant improvement in progression-free survival (PFS) by central review for patients treated with the combination whose tumors had programmed death ligand-1 positive (PD-L1+) expression greater than 1% (primary objective), as well as in the entire study population regardless of PD-L1 tumor expression (secondary objective).

According to the statistical analysis plan, if PFS was statistically significant in the PD-L1+ subgroup, then PFS in the entire study population was to be analyzed for statistical significance. JAVELIN Renal 101 will continue as planned to the final analysis for the other primary endpoint of overall survival (OS). No new safety signals were observed, and adverse events for Bavencio, Inlyta and Sutent in this trial were consistent with known safety profiles for all three medicines. The alliance of Merck and Pfizer intends to pursue a regulatory submission in the US based on these interim results, and these results will be discussed with global health authorities. A detailed analysis will also be submitted for presentation at an upcoming medical congress.

In December 2017, the US Food and Drug Administration (FDA) granted Breakthrough Therapy Designation for Bavencio in combination with Inlyta for treatment-naïve patients with advanced RCC. Despite available therapies, the outlook for patients with advanced RCC remains poor. Approximately 20% to 30% of patients are first diagnosed at the metastatic stage. The five-year survival rate for patients with metastatic RCC is approximately 12%.

JAVELIN Renal 101 is a global Phase III, multicenter, randomized (1:1) study investigating the efficacy and safety of Bavencio in combination with Inlyta as a first-line treatment option compared with Sutent monotherapy in 886 patients with advanced RCC across all risk groups. The primary objectives are to demonstrate that the combination is superior to Sutent monotherapy in prolonging PFS or OS in patients with PD-L1+ tumors. Bavencio was administered at 10 mg/kg IV every two weeks in combination with Inlyta at 5 mg orally twice daily; Sutent was administered at 50 mg orally once daily, four weeks on/two weeks off.

IKCS to be held in Miami, November 2-3

MIAMI—The 17th International Kidney Cancer Symposium, offering a comprehensive agenda and a broad spectrum of topics on diagnosis and treatment of renal cell carcinoma will be held at the National Doral Miami Hotel, November 2-3. The symposium, with an expected attendance of 400,

is sponsored by the Kidney Cancer Association. It will present analyses of emerging trends in RCC, Q&A sessions with key opinion leaders, and translational findings from clinical trials. Registration is available through the Kidney Cancer Association website: https://registeruo.niu.edu/iebms/reg/reg_p1_form.aspx?oc=40&ct=OTH&eventid=16044

Tivozanib hits another milestone with approval in Europe for advanced RCC

The European Commission (EC) has approved tivozanib (Fotivda) for the treatment of patients with advanced renal cell carcinoma (RCC), according to Aveo, the manufacturer of the pan-inhibitor of VEGF receptors, and its partner EUSA Pharma. The drug is specifically approved for the frontline treatment of adult patients with advanced RCC and for adults with advanced RCC who are VEGFR- and mTOR-inhibitor naïve following disease progression after one prior treatment with cytokine therapy.

The approval, which follows a positive recommendation from the European Medicines Agency's Committee for Medicinal Products for Human Use, is based on the phase III TiVO-1 trial, in which tivozanib reduced the risk of disease progression or death by over 20% versus sorafenib (Nexavar) in patients with advanced RCC who received up to one prior line of therapy (excluding targeted agents). Researchers at Institut Gustave Roussy are currently evaluating tivozanib in combination with nivolumab (Opdivo) for patients with advanced RCC in the phase I/II dose escalation/expansion TiNivo trial. Additionally, results are antic-

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Combination Immunotherapy and Targeted Therapy: Will New Combinations Raise the Tail of the Survival Curve?

Xin Gao, MD
Medical Oncologist
Claire and John Bertucci Center
for Genitourinary Cancers
Massachusetts General Hospital
Cancer Center
Boston, Massachusetts

Clinical trials investigating combinations of antibodies against the immune checkpoints PD-1 or PD-L1 plus targeted therapies against VEGF/VEGFR have shown promising anti-tumor activity over single-agent therapy in renal cell carcinoma (RCC). In addition to their proven clinical efficacy as single agents, each class of drugs has a distinct and potentially synergistic mechanism of action relevant to RCC biology. Several combinations are now in phase III evaluation in treatment-naïve metastatic RCC patients. This report summarizes the preclinical and clinical rationale underlying the use of such combination therapies and describes the latest combination trials, which may be transformative for the treatment of advanced RCC.

The therapeutic landscape for advanced renal cell carcinoma (RCC) has evolved rapidly in recent years, and additional clinical trials investigating combinations of immune checkpoint inhibitors with anti-angiogenic therapies are poised to continue to redefine the treatment paradigm. A randomized phase III study of the programmed death-ligand 1 (PD-L1) antibody atezolizumab in combination with the vascular endothelial growth factor (VEGF)-targeted antibody bevacizumab has already demonstrated clinical efficacy for a subset of patients with metastatic RCC (mRCC).[1] Furthermore, results from four large randomized phase III trials investigating various combinations of monoclonal antibodies against programmed cell death protein 1 (PD-1) or PD-L1 plus small molecule tyrosine kinase inhibitors (TKIs) of VEGF receptor (VEGFR) are highly anticipated as combination approaches work their way through rigorous review toward potentially reshaping the conventional sequential approach in the treatment of mRCC.

Combined targeting of PD-1/PD-L1 and VEGF/VEGFR is grounded in the basic biology of RCC. The highly immunogenic and vascular nature of RCC are well-known,[2,3] and it is logical that immunotherapeutic and anti-angiogenic approaches have yielded clinical success against this remarkably chemo-resistant neoplasm. The predominant histologic subtype – clear cell RCC (ccRCC) – is characterized by high proportions of immunogenic insertion and deletion mutations as well as increased immune infiltration compared to other human cancers.[4,5] Furthermore, a mutation in or inactivation of the von Hippel-Lindau (*VHL*) tumor suppressor gene is present in the vast majority of ccRCCs, leading to aberrant signaling via the hypoxia-inducible factor (HIF) transcriptional complex.[6,7] Altered expression of a multitude of HIF downstream genes, including VEGF, results in an adaptation to hypoxia through the formation of new blood vessels, increased glycolysis, and enhanced tumor proliferation and survival.[8]

While immunotherapies and anti-angiogenic therapies have individually become standard-of-care treatments for advanced RCCs, intriguing preclinical data have emerged in recent years to suggest beneficial effects of angiogenesis inhibitors on anti-tumor immunity. Tumor-associated blood and lymphatic vascular formation likely play key roles in promoting an immunosuppressive phenotype by modulating the recruitment, adhesion, trafficking, and function of immune cells in the tumor microenvironment.[9] Data from preclinical studies have built a framework for understanding the interaction between angiogenic signaling and anti-cancer

Keywords: Combination therapy, PD-1/PD-L1, immunotherapy, VEGR/VEGFR, anti-angiogenic therapy

Corresponding Author: Xin Gao, MD, Massachusetts General Hospital Cancer Center, Yawkey Building, Suite 7E, 55 Fruit Street, Boston, MA 02114 Tel: 617-724-4000 Fax: 617-643-1740

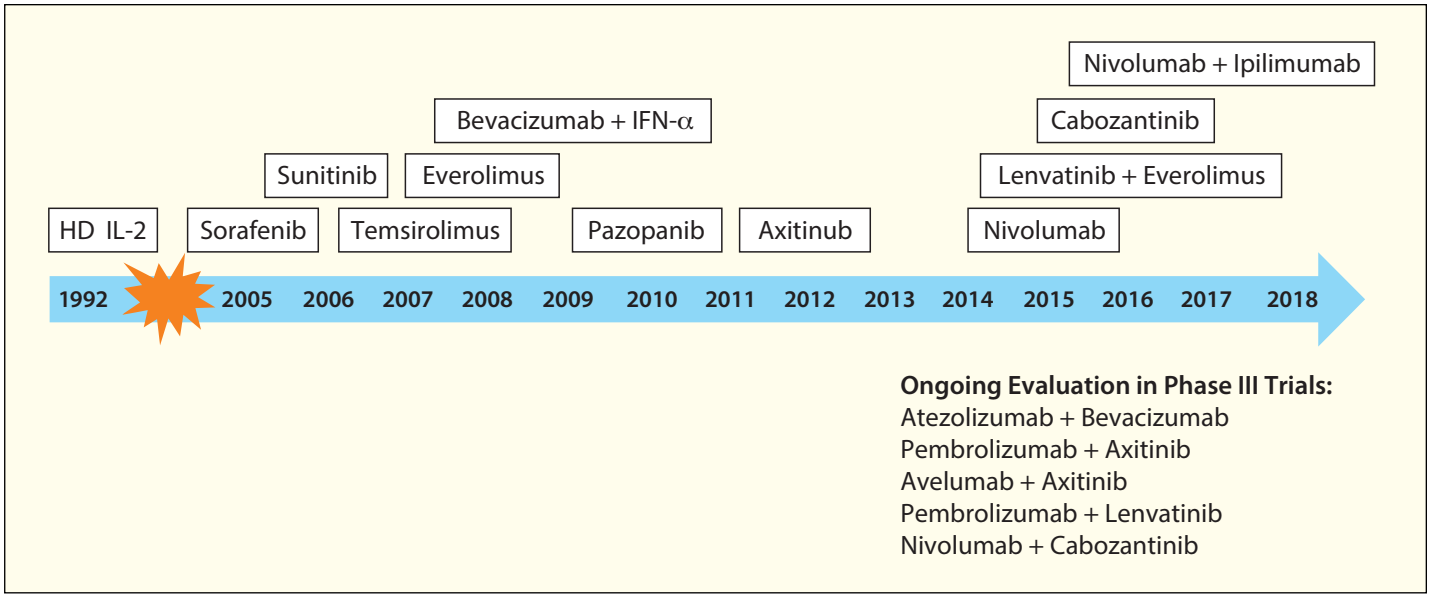

Figure 1. Current Treatment Landscape

immunity, ultimately providing a stronger rationale for the clinical use of combination therapies targeting the VEGF/VEGFR pathway and PD-1/PD-L1 immune checkpoints.[10] Due to the known clinical efficacy of separately targeting angiogenesis and immune checkpoints in mRCC, one of the key questions to be addressed by ongoing clinical trials is whether such combination therapies result in synergistic anti-tumor effects and improved clinical outcomes over sequential treatment (**Figure 1**).

VEGF Signaling and Anti-Tumor Immunity

The central roles of VEGF signaling and anti-tumor immunity in RCC have been well-established in preclinical models and from clinical experience with anti-angiogenic VEGF/VEGFR-targeted therapies, immune checkpoint inhibitors, and cytokine-based therapies. However, recent preclinical work has also suggested important interactions between VEGF signaling and the anti-tumor immune response. Broadly speaking, tumor-associated angiogenesis and lymphangiogenesis facilitate the establishment of an immunosuppressive tumor microenvironment via multiple mechanisms.[9] More specifically, VEGF signaling has been shown to inhibit the transcriptional maturation of dendritic cells that serve as antigen presenting cells for tumor-derived neoantigens,[11,12] promote the survival and proliferation of myeloid-derived suppressor cells that inhibit effector T cell function and induce regulatory T cell development within the tumor microenvironment,[13,14] and promote the expression of PD-1 and other inhibitory checkpoints involved in T cell exhaustion[15]. In addition, tumor-associated endothelial cells may induce defective clustering of cell adhesion molecules to inhibit lymphocyte adhesion and extravasation[16] and also selectively express the cell death mediator Fas ligand, which binds to Fas-expressing T cells to trigger apoptosis[17]. The preclinical data on the interactions between angiogenic signaling and cancer immunity and the clinical efficacy of independently targeting angiogenesis and immune checkpoints in RCC have led to efforts to evaluate whether combination therapy may result in synergistic anti-tumor effects and improved clinical outcomes.

The Landscape of Treatment Combinations

The treatment paradigm for mRCC is evolving from one dominated by single-agent anti-angiogenic agents and immunotherapies toward the adoption of combination regimens geared to achieve enhanced anti-tumor activity. Three combination regimens are already approved for the treatment of mRCC. The immunotherapy and anti-angiogenic therapy combination of interferon-alpha plus bevacizumab has been approved by the United States Food and Drug Administration (FDA) since 2008, though therapeutic efficacy is modest.[18,19] More recently, the combination of lenvatinib plus everolimus targeting VEGFR and mechanistic target of rapamycin (mTOR) and the immune checkpoint inhibitor combination of nivolumab plus ipilimumab were granted FDA approval in the second and first-line settings, respectively.[20,21]

Based on the preclinical rationale discussed previously and the development of multiple VEGF-targeted therapies and immune checkpoint inhibitors that confer improved clinical efficacies over the past decade, multiple combinations of anti-angiogenic agents plus immune checkpoint inhibitors are under investigation in late-phase clinical trials. Such combination strategies may ideally increase the number of long-term survivors and raise the tail of the survival curve, while moderating the additive or synergistic toxicities that may arise with immunotherapy and anti-angiogenic therapy combinations. The combination of atezolizumab plus bevacizumab is furthest into clinical development, having already met one of its co-primary endpoints of improved progression-free survival (PFS) in treatment-naïve mRCC patients with PD-L1-positive (PD-L1+) tumors in the phase III IMmo-

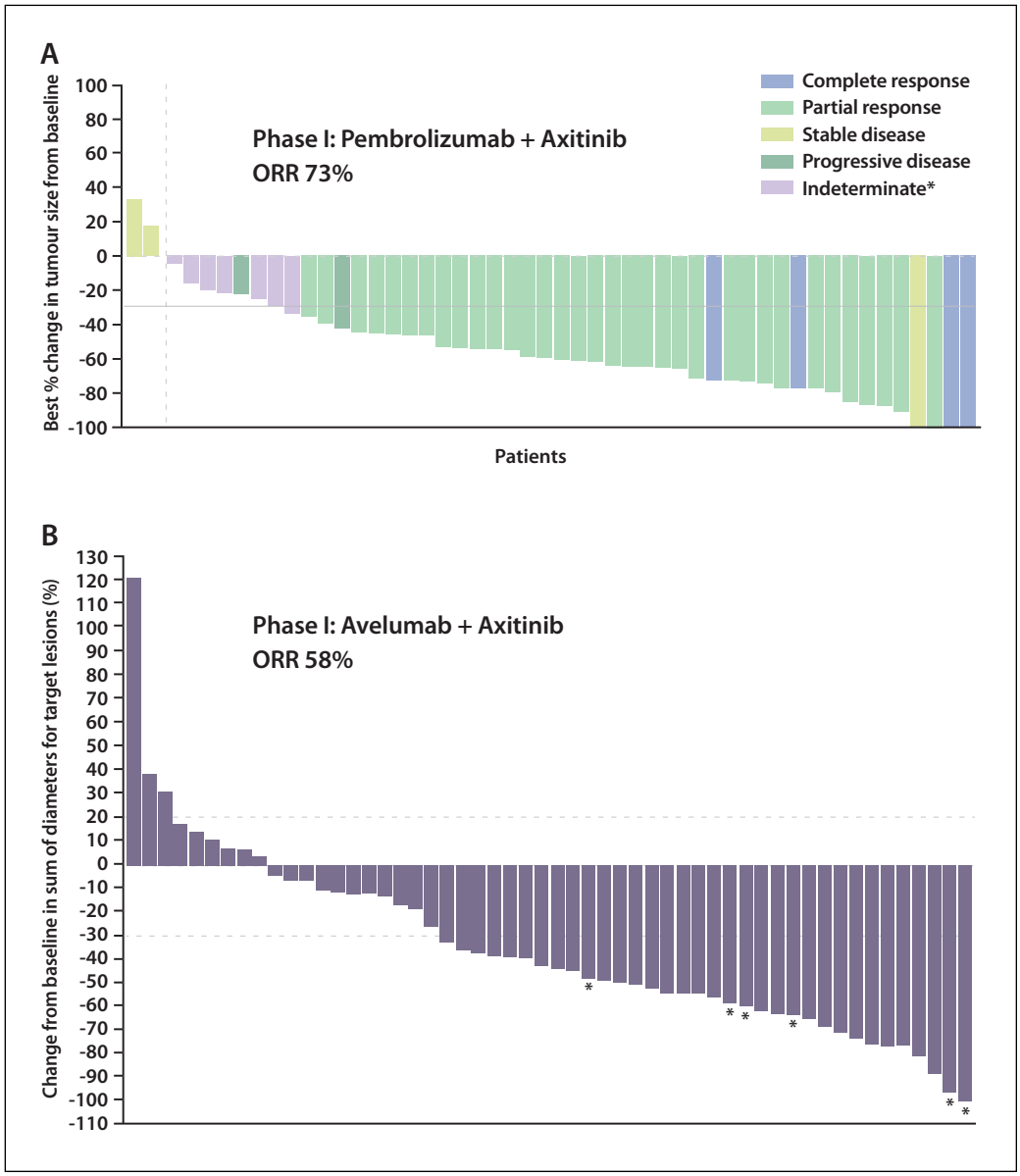

Figure 2. (A) Best percentage change in tumor size in the phase I study of pembrolizumab plus axitinib.[22] (B) Percentage change in sum of diameters of target lesions in the phase I study of avelumab plus axitinib.[23]

tion151 trial.[1] Phase I studies of several additional combinations in small numbers of patients have yielded promising early results exceeding what would be expected from anti-PD-1/PD-L1 or VEGFR TKI monotherapy (**Figure 2**):

- Pembrolizumab plus axitinib showed encouraging antitumor activity with an objective response rate (ORR) of 73% in previously untreated mRCC patients.[22]
- Avelumab plus axitinib showed an ORR of 58% in previously untreated mRCC patients.[23]
- Pembrolizumab plus lenvatinib showed an ORR of 63% in mRCC patients, 60% of whom had received prior anticancer therapy.[24]
- Cabozantinib plus nivolumab with or without ipilimumab showed an ORR of 54% in previously treated mRCC patients.[25]

Notably, combination therapies have also conferred additional toxicities. For example, development of immune checkpoint inhibitor combinations with pazopanib has been limited due to liver toxicity.[26,27] Furthermore, grade 3 or worse treatment-related adverse events (AEs) occurred in 65% of patients treated with pembrolizumab plus axitinib,[22] 58% of patients receiving avelumab plus axitinib,[23] 70% of patients receiving pembrolizumab plus lenvatinib,[24] and 62-71% of patients on cabozantinib plus nivolumab with or without ipilimumab in phase I testing.[25] As we move forward into phase III evaluations of these combinations, confirmation of clinical efficacy as well as of safety and tolerability will be eagerly awaited. Here, I describe the five combination regimens currently in randomized phase III clinical trials.

Atezolizumab plus Bevacizumab

IMmotion151 (NCT02420821) is the first randomized phase III trial of a PD-1/PD-L1 pathway inhibitor combined with an anti-VEGF agent in mRCC.[1] This trial randomized 915 treatment-naïve patients with predominantly clear cell or sarcomatoid histology advanced or mRCC to atezolizumab 1200 mg IV q3w + bevacizumab 15 mg/kg IV q3w or sunitinib 50 mg PO QD 4 weeks on/2 weeks off. Patients were stratified by PD-L1 status (<1% vs 1% or more expression on tumor-infiltrating immune cells) and prognostic risk groups. Co-primary endpoints included investigator-assessed PFS in PD-L1+ patients and overall survival (OS) in the intention-to-treat (ITT) population.

Results from the first interim analysis were presented at the 2018 Genitourinary Cancers Symposium. The study reached its co-primary endpoint of improved investigator-assessed PFS in the 362 patients with PD-L1+ disease who were treated with atezolizumab plus bevacizumab (HR 0.74, 95% CI 0.57-0.96; p = 0.02). Median PFS was 11.2 months in PD-L1+ patients treated with atezolizumab plus bevacizumab vs 7.7 months in patients treated with sunitinib. In addition, PFS in the ITT popu-

Table. Phase 3: ICI + VEGF/VEGFR Combinations

Treatments	Trial Identification	Enrollment	Primary Endpoints
Bevacizumab + Atezolizumab (every 3 weeks) vs Sunitinib (daily for 4 weeks on, 2 weeks off)	NCT02420821 IMmotion151	915 (Actual)	PFS in PD-L1+ OS in ITT
Axitinib + Pembrolizumab (every 3 weeks) vs Sunitinib (daily for 4 weeks on, 2 weeks off)	NCT02853331 KEYNOTE-426	862 (Actual)	PFS and OS in PD-L1+
Axitinib + Avelumab (every 2 weeks) vs Sunitinib (daily 4 weeks on, 2 weeks off)	NCT02684006 JAVELIN Renal 101	888 (Actual)	PFS and OS
Lenvatinib + Pembrolizumab (every 3 weeks) vs Lenvatinib + Everolimus (daily) vs Sunitinib (daily for 4 weeks on, 2 weeks off)	NCT02811861 CLEAR	735 (Estimated)	PFS
Cabozantinib (daily) + Nivolumab (every 2 weeks) vs Sunitinib (daily for 4 weeks on, 2 weeks off)	NCT03141177 CheckMate 9ER	630 (Estimated)	PFS

lation, a secondary endpoint, was also improved with atezolizumab plus bevacizumab vs sunitinib (median 11.2 vs 8.4 months; HR 0.83, 95% CI 0.70-0.97). Of note, an independent radiology committee assessed-PFS was also obtained and differed from the investigator-assessed PFS in the PD-L1+ population (median 8.9 vs 7.2 months). ORRs were not significantly different between atezolizumab plus bevacizumab vs sunitinib in both the PD-L1+ (43% vs 35%) and ITT populations (37% vs 33%). However, complete responses (CRs) were move common with atezolizumab plus bevacizumab vs sunitinib in both the PD-L1+ (9% vs 4%) and ITT populations (5% vs 2%). At the first interim analysis, OS data was immature, but suggestive of an encouraging trend favoring atezolizumab plus bevacizumab in both the PD-L1+ (HR 0.81, 95% CI 0.63-1.03; p = 0.09) and ITT (HR 0.68, 95% CI 0.46-1.00) populations. Follow-up of OS results will likely be crucial in the regulatory review of this regimen.

Atezolizumab plus bevacizumab was relatively well-tolerated compared to sunitinib, with grade 3-4 treatment-related AEs occurring in 40% vs 54% of patients, respectively. The most common grade 3-4 treatment-related AEs with atezolizumab plus bevacizumab included hypertension, proteinuria, and asthenia. Corticosteroids were given to 16% of patients treated with atezolizumab plus bevacizumab within 30 days of an AE of special interest. Treatment-related AEs led to therapy discontinuation in 12% of patients receiving atezolizumab plus bevacizumab and 8% of patients receiving sunitinib. Finally, quality-of life evaluations demonstrated significantly prolonged time to symptom interference with activities of daily living in patients treated with atezolizumab plus bevacizumab as compared to those treated with sunitinib (HR 0.56, 95% CI 0.46-0.68).

Interestingly, earlier evaluation of the combination of atezolizumab plus bevacizumab in a small number of mRCC patients demonstrated molecular and cellular changes consistent with the pre-clinical data that anti-angiogenic therapy modulates the anti-tumor immune response.[28] Tumor and blood based analyses after a 2 to 3 week lead-in of bevacizumab monotherapy demonstrated decreases in vascular markers as well as increases in gene signatures associated with T-helper 1 chemokines involved in lymphocyte trafficking, tumor MHC-I protein expression, and infiltration of tumor-specific T-cell clones. The subsequent addition of atezolizumab to bevacizumab resulted in anti-tumor activity that was associated with further increases in intra-tumor CD8+ T cells and the number of unique T-cell clones within the tumor microenvironment. Furthermore, the randomized phase II IMmotion150 study (NCT01984242) identified gene signatures associated with T-effector and myeloid inflammatory responses in pre-treatment tumor samples to significantly predict for response to atezolizumab plus bevacizumab vs atezolizumab monotherapy vs sunitinib.[29] The early studies on atezolizumab plus bevacizumab have provided thought-provoking insights into the pharmacodynamics of immune checkpoint and anti-angiogenic therapy that warrant further investigation.

Pembrolizumab plus Axitinib

While studies combining VEGFR-targeted TKIs with PD-1/PD-L1 checkpoint inhibitors have shown clinical activity in mRCC, some combinations have been limited by unacceptable toxicity, including severe liver function abnormalities and fatigue.[26,27] Many of the toxicities are thought to be related to the augmentation of off-target effects of multi-targeted TKIs by immune checkpoint inhibitors. In response, one approach has been to use a more specific inhibitor of VEGFR that may be better tolerated in combination with an anti-PD-1 drug. This was the rationale underlying a phase Ib trial of axitinib—a potent, selective inhibitor of VEGFR 1-3—in combination with pembrolizumab in treatment-naïve patients (n=52) with advanced ccRCC.[22]

The combination of pembrolizumab plus axitinib

demonstrated overall tolerability with fewer incidences of grade 3 or worse liver function abnormalities than was seen with prior combination studies with pazopanib or sunitinib. Dose-limiting toxicities were reported in 3 of 11 patients treated in the dose-finding phase of the study, and the maximum tolerated dose was determined to be pembrolizumab 2 mg/kg every 3 weeks and axitinib 5 mg twice daily. Grade 3 or higher treatment-related AEs were observed in 65% of patients, including hypertension, diarrhea, increased transaminases, hypothyroidism, and fatigue.

Pembrolizumab plus axitinib demonstrated encouraging anti-tumor activity. The proportion of patients who achieved an objective response was 73% (95% CI 59-84%), including 8% with a CR and 65% with a partial response (PR) at a median follow-up of 20.4 months. An additional 15% of patients had stable disease, and more than 90% of patients experienced some degree of tumor shrinkage. The median PFS was 20.9 months. The anti-tumor activity seen in the phase Ib study was superior to that expected from axitinib or anti-PD-1 monotherapy. A randomized phase III trial (KEYNOTE-426; NCT02853331) comparing the combination of pembrolizumab plus axitinib vs sunitinib monotherapy in treatment-naïve mRCC patients is underway and has reached its enrollment goal. The co-primary endpoints are PFS and OS in the PD-L1 positive population.

Avelumab plus Axitinib

JAVELIN Renal 100 was a phase Ib trial investigating the combination of the anti-PD-L1 antibody avelumab with axitinib in treatment-naïve patients (n=55) with advanced ccRCC.[23] Avelumab is a human IgG1 monoclonal antibody that not only targets the immune checkpoint protein PD-L1 but also mediates antibody-dependent cell-mediated cytotoxicity of cancer cells.[30]

The safety profile of avelumab plus axitinib was consistent with the known profiles of single-agent avelumab and axitinib. A dose-limiting toxicity of proteinuria was reported in 1 of 6 patients treated in the dose-finding phase. The maximum tolerated dose for the combination was determined to be avelumab 10 mg/kg every 2 weeks and axitinib 5 mg twice daily. Grade 3 or higher treatment-related AEs were reported in 58% of patients, most commonly hypertension, palmar-plantar erythrodysesthesia, and increases in transaminase, lipase, and amylase.

The combination of avelumab plus axitinib also demonstrated encouraging anti-tumor activity. Objective response was reported in 58% (95% CI 44-71%) of patients, including CR in 5% and PR in 53%. An additional 20% of patients experienced stable disease, resulting in a disease control rate of 78%. A majority of patients experienced early and durable responses. The anti-tumor activity of the combination in JAVELIN Renal 100 was superior to the expected activity of single-agent axitinib or anti-PD-L1 therapy. The randomized phase III trial JAVELIN Renal 101 (NCT02684006) is comparing avelumab plus axitinib against sunitinib monotherapy in treatment-naïve mRCC patients and has reached its accrual target. The co-primary endpoints are PFS and OS between the treatment arms.

Pembrolizumab plus Lenvatinib

The combination of pembrolizumab plus the multikinase TKI lenvatinib was evaluated in a phase Ib/II study in patients with selected solid tumors. Updated preliminary results from the ccRCC cohort (n=30) were reported at the 2018 ASCO Annual Meeting.[24] Unlike the phase Ib studies of pembrolizumab plus axitinib and avelumab plus axitinib in treatment-naïve patients, the early evaluation of pembrolizumab plus lenvatinib allowed for patients who previously received systemic therapies. Treatment-experienced patients accounted for 60% of the mRCC cohort. Pembrolizumab was administered at 200 mg every 3 weeks and lenvatinib administered at either 24 mg daily or 20 mg daily.

Grade 3 or higher AEs occurred in 73% of patients treated with the combination. The most common grade 3 or higher AEs included proteinuria, elevated lipase, hypertension, diarrhea, and fatigue. Dose adjustment or discontinuation due to AEs was common. Lenvatinib dose was reduced in 73% of patients, lenvatinib discontinuation in 20%, and pembrolizumab discontinuation in 27%.

The primary endpoint of ORR at 24 weeks was 63% (95% CI 44-80%) in the phase Ib/II study. Twenty-nine of the 30 patients experienced tumor shrinkage. Median PFS was 17.7 months. Anti-tumor activity appeared to be similar regardless of prior therapy or PD-L1 status. The phase III CLEAR trial (NCT02811861) is currently enrolling patients with treatment-naïve advanced ccRCC with randomization to pembrolizumab plus lenvatinib vs lenvatinib plus everolimus vs sunitinib. The dosing regimen of pembrolizumab 200 mg every 3 weeks and lenvatinib 20 mg daily was selected for the phase III study. The primary endpoint is to compare the PFS of pembrolizumab plus lenvatinib or lenvatinib plus everolimus vs sunitinib.

Nivolumab plus Cabozantinib

The combination of cabozantinib plus nivolumab with or without ipilimumab was evaluated in a phase I study that enrolled patients with a variety of metastatic genitourinary cancers.[25] Preliminary results were presented at the 2018 Genitourinary Cancers Symposium. A total of 75 patients were enrolled, including 14 patients with previously treated mRCC. Seven RCC patients accrued to the nivolumab plus cabozantinib cohort and 7 RCC patients accrued to the nivolumab plus ipilimumab plus cabozantinib cohort. A total of 7 dose levels were included in the study. All 7 RCC patients in the nivolumab plus cabozantinib combination received nivolumab 3 mg/kg every 2 weeks plus cabozantinib 40 mg daily, which was ultimately determined to be the recommended phase II dose for the doublet combination. All 7 RCC patients in the

triplet combination received nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks for four doses followed by nivolumab 3 mg/kg every 2 weeks, with 6 patients concurrently receiving cabozantinib 40 mg daily and 1 patient receiving cabozantinib 60 mg daily.

Grade 3 or 4 AEs were reported in 57% of all patients receiving doublet therapy and in 72% of all patients receiving triplet therapy. Common grade 3 or 4 treatment-related AEs included diarrhea, hypertension, fatigue, hypophosphatemia, hyponatremia, hypokalemia, lymphopenia, neutropenia, and elevations in transaminases, lipase, and amylase. Immune-related AEs were relatively uncommon with either doublet or triplet therapy.

At early follow-up (median 5.2 months), objective response was seen in 54% of patients in the RCC cohort. All responding patients experienced a PR. The remaining 46% of patients in the RCC cohort experienced stable disease. Patients with mRCC who experienced disease response appeared to have a prolonged duration of response, with median PFS estimated at 18.4 months (95% CI 6.4-18.4). The study investigators did not present data on RCC responses by doublet vs triplet therapy. The ongoing phase III CheckMate 9ER trial (NCT03141177) is comparing the combination of nivolumab plus cabozantinib vs sunitinib in treatment-naïve patients with advanced ccRCC. The primary endpoint is PFS of the treatment arms.

Combination Therapy vs Monotherapy: Is More Always Better?

The early data from combinations of immune checkpoint inhibitors plus anti-angiogenic therapies indicate that combination treatments may result in improved clinical efficacy as well as the potential for enhanced toxicities. Studies of immune checkpoint inhibitor monotherapy in advanced RCC and other tumors have demonstrated clinical activity in addition to a favorable toxicity profile.[31-33] For example, preliminary results from the phase II KEYNOTE-427 study of first-line pembrolizumab monotherapy in advanced ccRCC patients have shown an ORR of 38%, including 3% with CR and a majority of responding patients having ongoing responses at 12 months of follow-up. Long-term follow-up results from KEYNOTE-427 and data from the ongoing phase III combination studies in RCC may provide additional insights into the additive benefit anti-angiogenic agents to immune checkpoint inhibitor monotherapy. Survival data will be important in assessing the benefits of frontline combination therapy relative to sequential treatment with immune checkpoint inhibitors and VEGFR TKIs. It is possible that some patients may respond well to single-agent treatment and may be spared the additive toxicities of combination therapies, while other patients may require combination approaches to obtain clinical benefit. Biomarker analyses such as PD-L1 expression have been incorporated into all of the ongoing phase III studies. Further development of candidate predictive biomarkers such as angiogenesis- and immune-associated gene expression profiling[29] and tumor mutational burden[34] may provide guidance on optimizing treatment strategies for mRCC patients.

Conclusion

Combinations of immune checkpoint inhibitors plus anti-angiogenic therapies are advancing rapidly through clinical evaluation in mRCC, supported by preclinical data suggesting biological synergism and by the proven clinical efficacy of each therapeutic approach independently. Multiple early-phase clinical trials have demonstrated favorable anti-tumor activity and manageable safety profiles of combination therapies, and five large randomized phase III studies involving distinct treatment combinations are ongoing in treatment-naïve mRCC patients. The combination of atezolizumab plus bevacizumab has achieved one of its co-primary endpoints of improving PFS in patients with PD-L1+ tumors. With regulatory review of atezolizumab plus bevacizumab expected in the near future, results of survival data in follow-up will be key in further informing the role of this combination in the treatment of mRCC patients. Efficacy and safety results from four additional randomized phase III trials of VEGFR TKI plus anti-PD-1/PD-L1 therapy are also forthcoming. Ultimately, these studies have tremendous potential to transform the standard-of-care treatment for advanced RCC from one of sequential therapies to one of combination regimens that meaningfully improves the lives of kidney cancer patients.

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GUEST EDITOR'S MEMO

(continued from page 70)

by engaging commercial companies. However, how tumor profiling influences decision making and outcome in RCC is unclear. The issues of heterogeneity and tumor evolution also remain a trap on our journey to treatment, as often analyzed specimens come from a small component from the archival nephrectomy specimen. To overcome these barriers, understanding the disease at time of treatment decisions may be critical to determine if new mutations have developed and been selected for.

In a hypothesis-generating report Pal, et. al. looked at circulating tumor DNA (ctDNA) from a nationwide cohort of 220 consecutive patients with mRCC. Results suggest that the acquisition of additional genomic alterations can be a mechanism of resistance to therapy that hopefully could be targeted in the future. The noninvasive nature of ctDNA testing makes it an attractive method of obtaining real time genomic data as compared to serial biopsies of metastatic sites progressing through therapy. It also provides insight into acquisition of additional driver alterations during the course of tyrosine kinase therapy, which if confirmed may suggest a role for therapy prior to checkpoint inhibitors to increase immunogenicity and perhaps improve response to therapy. As increased genomic alterations can be a surrogate for mutational burden, shown to be correlated with increased neoantigen formation and improved response to immunotherapies, these insights may suggest a role for TKI prior to immune checkpoint inhibitors. The article in this issue by Drs. McGregor, Choueiri, and Flippot briefly covers this topic and reports and explores how this emerging biomarker may be an exciting avenue for further biomarker work.

I hope I have provided you a taste of some of the exciting topics to be covered in depth at the IKCS in November. Attendees at the symposium will come away with not only new insights on this subject but on many other findings with translational impact. These include point-counterpoint discussions and Q&A sessions on highly controversial areas, from the bench to the bedside. There is still time to register and make plans to attend the most comprehensive kidney cancer meeting of the year. You can find details by going to the Kidney Cancer Association website: https://www.kidneycancer.org/event/17th-international-kidney-cancer-symposium. See you in Miami!

Brian M. Shuch, MD
Guest Editor

Evolving Role of TKI Monotherapy in Front Line Metastatic Clear Cell RCC

Bradley A. McGregor, MD
Clinical Director
Lank Center of Genitourinary Oncology
Dana-Farber Cancer Institute
Boston, Massachusetts

Ronan Flippot, MD
Lank Center of Genitourinary Oncology
Dana-Farber Cancer Institute
Boston, Massachusetts

Toni Choueiri, MD
Director, Lank Center for
Genitourinary Oncology
Dana-Farber Cancer institute
Boston, Massachusetts

Tyrosine kinase inhibitors (TKI) directed against the Vascular Endothelial Growth Factor (VEGFR) were unquestionably the gold standard for front-line therapy in advanced renal cell carcinoma for years. Results from combination immunotherapy trials have challenged this approach. The field is in flux as we await data from several ongoing already accrued phase 3 trials comparing the combinations of immunotherapy and VEGF/VEGFR inhibitors with TKI monotherapy. Nevertheless, it is important to revisit guidelines on the use of front-line TKI monotherapy, not only to identify special considerations and recognize subsets of patients who could still benefit from them, but also to consider how other hypothesis-generating studies could further refine current strategies in the context of biomarkers development.

As the biology of renal cell carcinoma (RCC) has unraveled, the molecular rationale for the use of targeted therapy has been clearly delineated in numerous reports. With the recognition that the majority of sporadic clear-cell RCC (ccRCC) tumors are characterized by VHL tumor suppressor gene inactivation leading to VEGF overexpression, small molecules with inhibitory effects against the VEGF receptor transformed the landscape and displaced cytokine therapies, established during the 1990s as the first-line standard of care. As such, tyrosine kinase inhibitors (TKIs), initially sunitinib and pazopanib and more recently, cabozantinib, profoundly affected the management of first line advanced RCC, ushering in new treatment algorithms.

Keywords: tyrosine kinase inhibitor, monotherapy, front-line, prognostic classification, IMDC model, sunitinib, cabozantinib.

Corresponding Author: Bradley A. McGregor, MD, Dana-Farber Cancer Institute, 450 Brookline Avenue, Boston MA, 02215
Email: Bradley_McGregor@DFCI.HARVARD.EDU

With new combinations of immunotherapies with and without VEGF/VEGFR targeted agents showing promising results in the first-line setting, it is tempting to suggest that the era of TKI monotherapy is over (**Figure**). Already, the combination of nivolumab and ipilimumab has been approved by the FDA for the first line treatment of those with poor or intermediate risk RCC. As the time of writing of this article, two large phase 3 trials of atezolizumab or avelumab (both PD-L1 inhibitors) in combination with VEGF inhibitors met their primary end- point of superiority in term of progression-free survival (PFS) over single agent sunitinib.[1,2] Yet, depending on prognostic factors and patient risk profiles, TKI monotherapy may still play a role in the frontline setting. This report will review most recent trials evaluating frontline TKIs, offering perspectives on their sustained importance in the therapeutic sequence and essential considerations about patient selection.

Prognostic Considerations

The importance of TKI monotherapy for metastatic ccRCC should be put into perspective with the IMDC or MSKCC prognostic classifications,[3] of which the IMDC was the first validated model to assess overall survival (OS) in the era of VEGFR-directed TKIs. Since then, numerous clinical trials of TKI monotherapy and immunotherapy stratified the study population according to these prognostic factors.

In the IMDC model, 6 factors were independently associated with poor survival: hemoglobin less than the lower limit of normal, corrected calcium greater than the upper limit of normal, Karnofsky performance status less than 80%, time from diagnosis to treatment of less than 1 year, neutrophils greater than the ULN and platelets

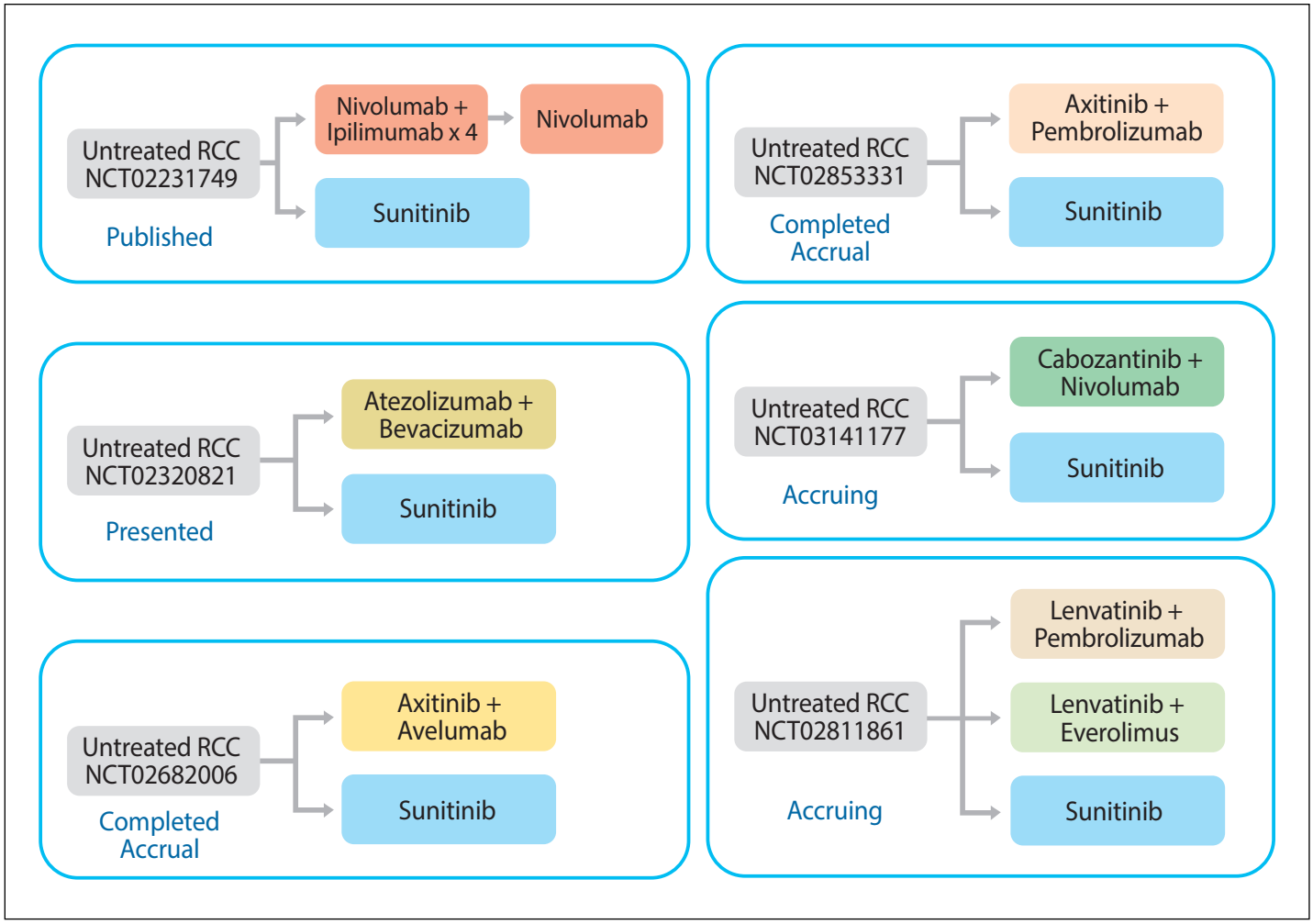

Figure. Ongoing trials in front line ccRCC.

greater than the ULN. Patients were segregated into three risk categories: the favorable-risk group (no prognostic factors; n = 133), in which median OS (mOS) was not reached and 2-year OS (2y OS) was 75%; the intermediate-risk group (one or two prognostic factors; n = 301), in which mOS was 27 months and 2y OS was 53%; and the poor-risk group (three to six prognostic factors; n = 152), in which mOS was 8.8 months and 2y OS was 7%. All these prognostic factors may reflect increased tumor burden, aggressive tumor biology, and/or paraneoplastic processes, which might account for their high discriminatory power.[4–6] This classi- fication is widely applicable, as it involved real-world patients from multiple sites, and was validated in additional cohorts and prospective clinical trials.[7,8]

Sunitinib vs Pazopanib vs Cabozantinib: TKI Monotherapy Comparisons, Criteria for Selection

TKI monotherapy has been the mainstay of therapy for over 10 years. Evidence is still accumulating from prospective trials on the relative merits of these three TKIs, while emerging data highlight their distinct activity and safety profiles. Until 2017, sunitinib and pazopanib were the two approved agents used most often in the first-line setting. The COMPARZ phase 3 non-inferiority study showed that pazopanib was not inferior to sunitinib in term of PFS (primary endpoint) and OS (secondary endpoint).[9] Objective responses were higher in the pazopanib group. Although the study found similar rates of dose reduction and drug discontinuation due to adverse events, differences were revealed in safety profiles: patients assigned to pazopanib had less fatigue, gastrointestinal adverse events, hand-foot syndrome, mouth sores, but experienced higher rates of liver toxicity. Eleven out of 14 quality of life metrics favored pazopanib over sunitinib. Therefore, the safety profile would be key to determine therapeutic strategies in the setting of similar efficacy.[10,11]

Further evidence regarding the importance of patient-reported outcomes and how they can help treatment choices came from the phase II cross-over trial PISCES.[12] This study raised the importance of patient evaluation to assess differences in tolerability that may not be accurately captured by the standard measures used for adverse event reporting. This could be especially true in the case of low-grade but chronic toxicities, that can still impact the quality of life of patients.[13] Pazopanib was preferred

to sunitinib in 70% of patients and 67% of physicians, given quality-of-life and fatigue concerns.

Critics of the study point out that sunitinib was given on a 4/2 schedule in both PISCES and COMPARZ, while alternative schedules have since been evaluated to improve toxicity. Nonetheless, a randomized phase 2 trial comparing continuous dosing of sunitinib 37.5 mg daily with conventional dosing showed a trend towards improved PFS with traditional schedule (9.9 vs 7.1 months, hazard ratio (HR) 0.77; 95% CI, 0.57 to 1.04; $P = .090$), with no difference in side effects profile, or patient-reported kidney cancer symptoms.[14] However, a randomized phase 2 trial comparing a 2/1 dosing schedule to traditional dosing showed improved failure free survival at 6 months (63 vs 44%) as well as less toxicities with alternative dosing.[15] Another phase 2 study exploring the 2/1 dosing schedule did not meet the primary end point of decreased grade 3 toxicity though it was associated with a lack of grade 4 toxicity and a high response rate of 57%. Given the desire to maximize dosing, it is appealing to start with the highest dose possible. The pros- pective phase IIB SURF trial [NCT02689167], accruing now, starts with traditional dosing; when toxicities arise, patients are randomized to sunitinib 37.5 mg on a 4/2 schedule vs sunitinib 50 mg on a 2/1 schedule.

Cabozantinib vs Sunitinib in the CABOSUN Trial

Cabozantinib is a VEGFR inhibitor that also targets multiple kinases, including MET and AXL receptors. MET is a receptor to the hepatocyte growth factor (HGF), which activates pathways involved in survival, proliferation and invasion. MET can also regulate cortical bone osteogenesis,[16] making it an interesting target in the context of bone metastases. AXL is binds to growth arrest specific 6 (GAS6), involved in growth, migration and differentiation in multiple cell types. Expression of MET and AXL have been associated with tumor progression and resistance to VEGF-pathway inhibition in preclinical models, and adverse outcomes in clinical studies. Initial approval for cabozantinib came from the VEGF-refractory setting with METEOR, a randomized phase 3 trial that compared the efficacy and safety of cabozantinib versus the mTOR inhi- bitor everolimus.[17] Later on, the randomized ALLIANCE phase 2 trial CABOSUN evaluated cabozantinib against sunitinib in the first-line setting, and a recent update evaluated the primary endpoint of PFS by central review.[18,19] Among 157 patients, cabozantinib significantly prolonged PFS compared with sunitinib in poor or intermediate risk patients, from 5.3 to 8.6 months. Toxicity rates were comparable between the two arms, with increased grade 3/4 fatigue and hematologic abnormalities with sunitinib, but increased liver function test abnormalities, anorexia and dysgeusia with cabozantinib. With a median follow-up of 34.5 months, median OS was 26.6 months (95% CI 14.6-not estimable) with cabozantinib and 21.2 months (95% CI 16.3-27.4) with sunitinib (HR 0.80 [95% CI 0.53-1.21]. Another element that might account for the improved PFS of cabozantinib over sunitinib is the low performance of the sunitinib arm, as prior studies rather demonstrated longer PFS with sunitinib in the first line setting. However, the population of CABOSUN had only patients harboring intermediate or poor risk disease, 30% having bone metastases and 13% with a performance status of 2. Notwithstanding this selected population, the recent FDA approval of cabozantinib was granted to all patients presenting with untreated advanced RCC independently of risk classification.

The Importance of Patient Classification

The importance of patient stratification to determine the best therapeutic approach was highlighted by the CheckMate 214 trial of nivolumab and ipilimumab vs sunitinib.[20] The coprimary endpoints were objective responses rate, PFS, and OS among IMDC intermediate- and poor-risk patients. At a median follow-up of 25.2 months, nivolumab plus ipilimumab had a significant OS benefit over sunitinib among intermediate- and poor-risk patients: median OS was not reached with nivolumab plus ipilimumab vs 26.0 months with sunitinib (HR 0.63, 99.8% CI = 0.44–0.89, $P < .001$). Based on these results, the FDA granted approval to nivolumab plus ipilimumab for the treatment of intermediate- and poor-risk treatment-naive patients with advanced renal cell carcinoma.

However, the CheckMate 214 trial also demonstrated that prognostic risk strata differentially impacted the outcomes in each study arm. In the favorable-risk cohort (35 % of all patients by MSKCC) , the objective response rate was higher in sunitinib-trea-ted patients than in those receiving nivolumab plus ipilimumab—29% with nivolumab plus ipilimumab vs 52% with sunitinib ($P < .001$), although complete responses were higher with nivolumab and ipilimumab, observed in 11% vs 6% of patients respectively. Additionally, PFS favored sunitinib over nivolu- mab plus ipilimumab (25.1 months for sunitinib vs 15.2 months for nivolumab plus ipilimumab, $P < .001$). The near double improvement in PFS and ORR with sunitinib in the favorable risk patients is notable, though the marked improvement in CR with the combination arm can support this immunotherapy combination as an option for those with good risk disease despite its FDA label. The combination is not without its toxicities. While grade 3 and 4 toxicities were less frequent with nivolumab+ipilimumab (46 vs 63%), 60% of patients receiving the immunotherapy combination received corticosteroids in the course of their treatment; of those with immune related adverse events 35% required high dose (>40 mg per day of prednisone)

The IMmotion 151 phase 3 that evaluates the anti-PD-L1 atezolizumab plus bevacizumab sunitinib highlights the importance of VEGF/ VEGFR-targeted therapies in favorable risk patients.[1] In this study, atezolizumab plus bevacizumab provided a PFS improvement in PD-L1 positive advanced RCC compared to sunitinib (HR 0.74, $P = 0.02$), which was the primary endpoint of the study. The benefit of bevacizumab plus atezolizumab in IMmotion 151 was found to be consistent regardless of the risk

groups. Taken together, the recent results of CheckMate 214 and IMmotion 151 suggest that anti-angiogenic therapies can still have a place in the frontline setting.

The Role of PD-L1 Staining

PD-L1 staining by immunohistochemistry (IHC) to guide therapy in RCC remains controversial. In the second line setting, PD-L1 expression was shown to be associated with a poor prognosis independent of the treatment (nivolumab or everolimus).[21] In the CheckMate 214 trial, analysis of outcomes by PD-L1 expression status demonstrated again that PD-L1 expression was prognostic though the degree of benefit from the combination of nivolumab plus ipilimumab was noticeably different based on PD-L1 status. Using the Dako PD-L1 IHC 28-8 pharmDx test with a cutoff of 1% on tumor cells, PFS was markedly improved in PD-L1 positive patients treated with nivolumab plus ipilimumab compared to sunitinib, from 5.9 months to 22.8 months. No benefit was reported with the combination in the PD-L1 negative group (<1%), with respective PFS of 10.4 vs 11 months. However, OS benefit was maintained independently of PD-L1 status, though again the degree of benefit was more pronounced in the PD-L1 positive patients.

In the IMmotion 151 phase III study of atezolizumab and bevacizumab compared with sunitinib, treatment with atezolizumab and bevacizumab resulted in improved investigator-assessed PFS in PD-L1–positive patients, achieving the study's primary endpoint (11.2 vs 7.7 months, HR 0.74, 95% CI: 0.57-0.96, P = 0.02)[1] PDL-1 positivity was defined as ≥ 1% in the tumor infiltrating cells using expression by immunohistochemistry with the SP142 assay. Taken in aggregate, these studies indicate that the chance for improved efficacy may be higher in PDL-1 positive tumors in the frontline setting, at least with combination of nivolumab/ipilimumab and atezo-lizumab/bevacizumab, though responses are seen in PDL-1 negative tumors. Ongoing trials exploring different immune checkpoint and VEGFR inhibitors may also stratify patients using different PD-L1 tests and cutoffs for positivity. Thus, the role of PD-L1 as a predictive and prognostic biomarker may continue to evolve. As such, refined predictive biomarkers to select patients for VEGF-targeted therapy alone, checkpoint blockade, or combination therapy are warranted to inform treatment decision making.

Perspectives From Genomic Profiling

Genomic profiling continue to evolve in RCC; there are several biomarker driven trials currently open in non-clear cell RCC. SAVOIR explores the role of a pure MET inhibitor savolitinib vs sunitinib in those with MET-driven papillary RCC (NCT 03091192), while PAPMET is comparing PFS in patients with metastatic papillary renal cell carcinoma treated with sunitinib vs several MET (+/- VEGF) Kinase inhibitors (NCT 02761057). However, currently the role of universal tumor profiling in advanced ccRCC is unclear. In clinical practice it is most commonly used in later lines to try and find potentially targetable mutations. Several reports mention that tumors harboring mutations in the TOR/Akt/PI3K pathway may increase responses to mTOR inhibitors.[22,23] One report in advanced ccRCC showed that patients with PBRM1 mutations may respond better to immune checkpoint blockers.[24]

Gene expression signatures, while not readily available in clinical practice to date, may also help improve therapeutic strategies. The IMmotion 150 phase 2 trial included three cohorts: sunitinib, atezolizumab, atezolizumab plus bevacizumab.[25] Correlative analyses for biomarkers revealed that patients with a high angiogenic genes expression had better outcomes with sunitinib compared to the other 2 arms. Validation of genomic profiling to assess the optimal therapeutic sequence might come from prospective trials, such as the phase 2 BIONIKK trial, which will randomize patients to dedicated treatment arms according to their molecular profile (NCT02960906).

> "Novel treatment strategies involving the use of immunotherapeutic and targeted agents have ushered in a new era and challenged TKI monotherapy in the frontline setting, with combination therapies that will likely become the standard of care for most patients. However, TKI monotherapy may represent a preferred option in subtypes of patients in this setting."

Conclusion

Novel treatment strategies involving the use of immunotherapeutic and targeted agents have ushered in a new era and challenged TKI monotherapy in the frontline setting, with combination therapies that will likely become the standard of care for most patients. . However, TKI monotherapy may represent a preferred option in subtypes of patients in this setting. At this point, patient comorbidities, IMDC risk classification are critical to guide treatment strategies. Future clinical trials should help refine these classifications and help physicians achieve a more personalized approach for treatment strategies.

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The Landscape of Adjuvant Therapy: A Controversy in Search of a Consensus

Michael R. Harrison, MD
Associate Professor of Medicine
Division of Medical Oncology
Duke Cancer Institute
Duke University Health System
Durham, North Carolina

Numerous studies have taken aim at what still appears to be a moving target—optimal use of adjuvant therapy. The volume of literature on this treatment setting has grown rapidly in the past several years and ongoing studies will soon add to the wealth of information—often discordant—on the clinical dilemma in this disease space. A review of the key studies suggests overarching issues and the salient questions still to be addressed. Studies of immune checkpoint inhibitors provide a potential path forward.

Clinical decision making in the adjuvant therapy setting for renal cell carcinoma (RCC) remains challenging. Despite a dramatic evolution in therapy that has ushered in novel approaches in metastatic disease with the promise of improving outcomes in the adjuvant setting, it remains a hotbed of controversy with the results of pivotal trials decisively at odds with one another. The discrepancy in the results of these trials has not helped to resolve the unmet need for an effective strategy for high risk locoregional kidney cancer. There is still clinical equipoise as to whether targeted therapy improves outcomes significantly, highlighted by the placebo comparator (as opposed to sunitinib) in recently designed adjuvant trials. The topic of adjuvant therapy for high risk localized RCC remains a controversy in search of a consensus.

The 5-year survival rate is 53% for locoregional (stage III) disease and 8% for metastatic (stage IV) disease.[1] Overall, locoregional disease is diagnosed in 16% of patients with RCC, and the unmet need is plainly evident when one considers that up to 40% of these patients have a relapse with metastasis after nephrectomy.[2,3] This relapse risk has been assessed with validated models, including the University of California Los Angeles Integrated Staging System (UISS). One of the challenges in validating an effective adjuvant therapy is the relatively long duration to observe a benefit in disease-free survival: the S-TRAC Trial, for example, required a median of 5.4 years follow up before a benefit became apparent. Practically speaking, this means that patients were enrolled to the study from September 2007 to April 2011. The study was presented at a scientific congress and published simultaneously in October 2016, and sunitinib received FDA approval in November 2017.

Keywords: adjuvant therapy, locoregional, cytokine therapy, S-TRAC, ARISER, ASSURE, PROTECT, disease-free survival, sunitinib, pazopanib.

Corresponding Author: Michael R. Harrison, MD, Duke Cancer Center
20 Duke Medicine Circle Durham, NC 27710
Email: michael.harrison@duke.edu

Initial Results in Cytokine Era Disappointing

Initial efforts to improve the prognosis in the adjuvant setting began in the cytokine era. Prior to the approval of targeted agents, IFN-alpha was used as a reference standard for phase III studies in metastatic (mRCC). IL-2 was approved for mRCC in 1992, and in comparison with IFN-alpha, the agent had greater potential for inducing durable responses (occurring in roughly 5-10% of treated patients.[4] However, the use of IL-2 has generally been restricted to younger patients with good performance status and more limited metastases.[5]

These earlier efforts in the cytokine era, however, met with a lack of success.[5] A study led by the Cytokine Working Group, for example, is typical of the disappointing results: the study was prematurely closed after an interim analysis suggested futility for the primary endpoint—2-year DFS. One of the earlier trials of a targeted approach for adjuvant therapy was ARISER.[6] It examined a carbonic anhydrase IX inhibitor (girentuximab), a chimeric monoclonal antibody that binds a cell surface glycoprotein ubiquitously expressed in clear cell RCC. Adjuvant girentuximab failed to improve disease-free or overall survival vs placebo in a cohort of patients with fully resected, high-risk clear cell renal cell carcinoma. Although ARISER was disappointing, it signified a transition to a new generation of studies and an evolution in the rationale for treatment as cytokine therapy, at least in the adjuvant setting, began to fade because of a lack of efficacy. As the cytokine era was brought to a close by the emergence of novel targeted therapies, signaling the beginning of the targeted therapy era in 2006, investigations turned toward the use of antiangiogenic strategies. The proven ef-

Table. Differences between the S-TRC and ASSURE studies

Category and variable	ASSURE [21]	S-TRAC [4]
Study conduct		
Study sites (*n*)	226	97
Patients treated with sunitinib/placebo (*n*).	647/647	309/306
Regions	USA, Canada	America, Europe, Asia, Australia, Middle East
Treatment arms (n)	3	2
Blinded independent central review of scans		
At baseline	No	Yes
At recurrence	No	Yes
Stratification	1. Histology (CC vs NCC). 1. ECOG PS (<2 vs 2) 3. ECOG PS (0 vs 1) 4. Risk category	2. Sirgery (laparoscopic vs open) 2. Risk category 3. Country
Patient characteristics		
CC RCC (%)	79	>99
NCC RCC	21[a]	<1
Risk groups included	≥T1b G3-4 and/or N+ [b]	≥T3 and/or N+ [c]
RCC stage 1-11 (%)	33[a]	0
Treatment		
Completed the full 1-yr treatment (%)	49	56
Dose Administered		
Starting does levels	2 (50 mg and 37.5 mg)	1 (50 mg)
Sunitinib starting dose of 50 mg/d (%)	70[d]	100
Minimum dose reduction allowed <mg)	25.0	37.5
Median number of cycles (n)	8	9
Median actual cumulative	6800	9638
Sunitinib exposure, mg (IQR)	(2600-9900)	(5550-12200)
Safety		
Discontinuations due to AEs/refusal/other (%).	41	32

AEs (%)	G3	G$	G5	G3	G4	G5
Hypertension	17	<1	0	8	0	0
Fatigue	17	1	0	4	<1	0
Hand-foot skin reaction	15	0	0	15	1	0
Diarrhea	10	0	0	4	0	0
All AEs	57	5	1	48	12	0

AE = adverse events; CC = clear cell; ECOG PS = Eastern Cooperative Oncology Group performance status; G = grade; IQR = interquartile range; NCC = non–clear cell; RCC = renal cell carcinoma.
[a] In the sunitinib arm.
[b] pT1b, G3–4, no or undetermined nodal involvement, no metastasis, or any T, any G, with local nodal involvement (fully resected), and no metastasis.
[c] T3 or T4, no or undetermined nodal involvement, no metastasis, or any T stage with local nodal involvement; and for all patients, any Fuhrman grade and any ECOG PS.
[d] The remaining patients started at a reduced dose of 37.5 mg.

ficacy of antiangiogenic therapies, including sunitinib and pazopanib in metastatic RCC, supports the evaluation of these drugs as adjuvant therapy.

This report seeks to present a fair and balanced view of the latest findings from pivotal trials on the use of targeted therapies in the adjuvant setting. As Haas et al point out, RCC is arguably the most biologically rational setting in which to assess the adjuvant role of anti-angiogenic therapies, given their single agent activity in patients with advanced disease.[7] To date, sunitinib is the only one of these agents given FDA approval as adjuvant therapy for RCC based on the positive results of the S-TRAC phase III trial. Meanwhile, three other phase III trials of adjuvant antiangiogenic strategies have been negative. Among the key questions to address is what accounts for the discrepancy in results from the major. Why, for example, do the results from S-TRAC, the second adjuvant trial reported in the targeted therapy era, suggest a benefit from the use of adjuvant sunitinib while the data from ASSURE, the first trial reported in the targeted therapy era, indicate no difference in the primary endpoint of disease free-survival[7]? The discrepancies be-

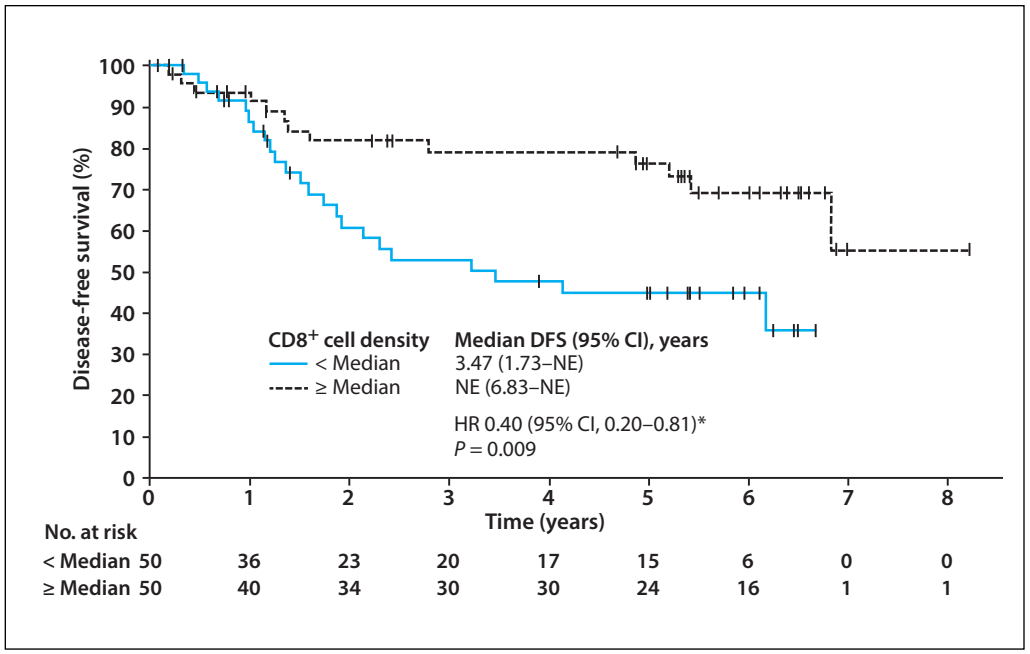

Figure 1. CD8+ T-cell density identifies a group of patients with prolonged DFS upon sunitinib treatment. The Kaplan-Meier curve of DFS per tumor CD8+ T-cell density: comparison of < vs ≥ median CD+ T-cell density in the sunitinib treatment group.

tween the ASSURE trial and S-TRAC resulted in uncertainty regarding the benefit of adjuvant sunitinib, with advocates and skeptics focusing on methodological details as limitations of each study. This uncertainty only continued with the negative results of two subsequent trials, PROTECT and ATLAS.

ASSURE and S-TRAC: A Mixed Picture for Use of Antiangiogenic Therapy

In deciphering the different messages from each of these two trials, Lenis et al[8] highlighted these key points:

- The first key difference is the baseline risk of the study populations: ASSURE included patients with pT1b or greater grade 3 to 4 disease, whereas S-TRAC included more advanced locoregional (pT3 or greater disease).
- In ASSURE more than a third of the patients had high grade T1 or T2 disease and would not have met the inclusion criteria of S-TRAC. This can be seen in the median DFS of the placebo groups—one year longer in ASSURE.
- Because S-TRAC had a higher risk population, Lenis et al suggest that they were more likely to have had micrometastatic disease and potentially more to gain from adjuvant therapy.
- The percentage of patients with nonclear cell histology is also a factor—20% in ASSURE. VEGF inhibitors have a poorer track record in nonclear cell histology mRCC (lower response rates and progression free survival compared with clear cell histology mRCC).
- Dosing adjustments were also identified as a potential factor. ASSURE had a decreased dose exposure to sunitinib, potentially reducing the observed efficacy of the active treatment arm to the control group.
- Lenis et al underscore the importance of optimal patient selection as the key factor in delineating whether patients are likely to benefit from adjuvant sunitinb. Thus, patients with high risk locoregional clear cell cancer may be offered the option of adjuvant sunitinib for 1 year following surgery in the context of known risk of side effects.

S-TRAC Produced Positive But Controversial Outcomes

Drawing on updated information on S-TRAC and providing further evidence for its benefits, Motzer et al[9] offered additional insights on the relationship between baseline factors and DFS, pattern of recurrence, and new overall survival. In addition to the positive outcome in the overall population of the S-TRAC study, the majority of subgroups defined according to baseline characteristics experienced longer DFS on sunitinib compared to placebo, including the prespecified subgroup of patients with higher risk of recurrence (defined as T3, no or undetermined nodal involvement, Fuhrman grade≥ 2, and ECOG PS≥ 1; or T4 and/or nodal involvement) compared to the overall population, as well as the subgroup of patients with Fuhrman grade 3/4. Still unresolved, however, is the impact of adjuvant sunitinib on OS. The updated data from Motzer et al were not mature enough to derive a reliable conclusion on this issue as there were still relatively few events (i.e. deaths) Nevertheless, this study did not observe a detrimental effect on OS and it should be noted that the trial was not powered to show an OS benefit.

The controversial nature of adjuvant therapy was again reflected in an updated analysis of the ASSURE trial focusing on a high risk, clear cell histology subset similar to that in S-TRAC.[7] The key question asked by these investigators was whether high-risk clear cell RCC patients (pT3 or more or node-positive) receiving sunitinib or sorafenib have improved DFS, and does the dose intensity of either drug affect outcome? This study sought to investigate whether the results from S-TRAC could be achieved in a similar subset in ASSURE. DFS and OS at 10 years postactivation were calculated for 1069 patients in US and Canadian cooperative groups with high-risk patients who had ccRCC histology and pT3, pT4, or node-positive disease accrued between 2006 and 2010. to the double-blind randomized placebo-controlled phase 3 trial. The groups included 243 [67.9%] men, 115 [32.1%] women) who received sunitinib; 248 [69.9%] men, 107 [30.1%] women) received sorafenib, and 356 received

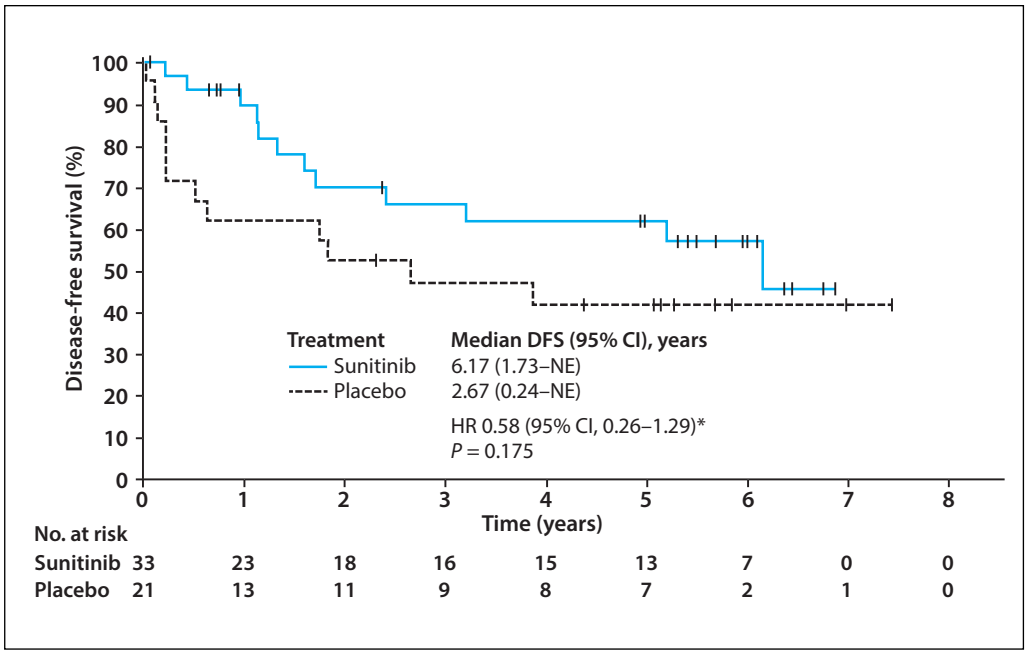

Figure 2. Curve of DFS in patients with PD-L1 positive tumors in the sunitinib vs placebo groups. Sunitinib-treated patients had more prolonged DFS.

placebo as adjuvant therapy. The mean age for each group was 58.3 (10.6) years, 56.8 (10.3) years, and 57.5 (10.4) years, respectively. Five-year DFS rates were 47.7%, 49.9%, and 50.0%, respectively for sunitinib, sorafenib, and placebo (HR, 0.94 for sunitinib vs placebo; and HR, 0.90; 97.5%CI, 0.71-1.14 for sorafenib vs placebo) with 5-year OS of 75.2%, 80.2%, and 76.5 (HR, 1.06; 97.5%CI, 0.78-1.45; P = .66, sunitinib vs placebo; and HR, 0.80; 97.5%CI, 0.58-1.11; P = .12 for sorafenib vs placebo). The authors also concluded that lack of difference in DFS and OS was not altered by prognostic category or dose intensity in patients with high risk, clear cell histology RCC.

Subsequent Analyses Focused on Adverse Events and Immune Correlates in S-TRAC

Despite the analysis by Haas et al, the debate has continued to seesaw with the publication of other findings, one current study related to the management of adverse effects of sunitinib and the other exploring whether immune biomarkers could be predictive for DFS in high-risk patients in S-TRAC. A study by Staehler et al[10] found that AEs in S-TRAC were predictable, manageable, and reversible via dose interruptions, dose reductions, and/or standard supportive medical therapy. Patients on sunitinib did report increased symptoms and reduced HRQoL, but these changes were generally not clinically meaningful, apart from appetite loss and diarrhea, and were expected in the context of known sunitinib effects. Management of sunitinib AEs has been continuously evaluated in numerous studies over the past decade, but this paper, focusing primarily on the S-TRAC database, could have implications for interpreting the S-TRAC results and adopting strategies to minimize significant AEs affecting whether patients continue on the drug.

In another study conducted by George et al,[11] a prospectively designed exploratory analysis of tissue samples from a subset of patients from S-TRAC, identified predictive biomarkers that could facilitate future patient selection for adjuvant sunitinib and facilitate an improved understanding of mechanisms of interaction that might explain the durable treatment effect, potentially leading to future combination approaches. Tumor tissue expression levels of CD4, CD8, CD68, and PD-L1 using IHC staining of formalin-fixed, paraffin-embedded tissue blocks were compared with efficacy outcomes. The observed association between higher CD8+ T-cell density in tumor tissue with longer DFS with sunitinib, but not placebo, suggested predictive potential of CD8+ T-cell density, which would warrant further independent cohort validation studies. The prognostic value of PD-L1 expression in primary tumors in this setting should also be further explored, according to another report.[12]

CD8+ T-cell density is interesting for two reasons. First, this is a measure of T-cell recognition and infiltration of the tumor and suggests a level of immune activation de novo. Although it is not prognostic, the predictive association with sunitinib treatment would suggest that CD8+ T cells may play a role in the treatment effect of sunitinib (**Figure 1**). In the setting of VEGF/VEGFR inhibition and tumor hypoxia, CD8+ T cells might be able to better recognize tumors through the exposure of neoantigens. Still other implications from the report by George et al is that the CD8+ T-cell infiltration and subsequent activation could potentially explain the lasting treatment effect beyond 1 year associated with patients in the sunitinib treatment group (**Figure 2**). The second interesting point of this predictive association between CD8+ T cells and sunitinib treatment is the link between the immune system and antiangiogenic therapy. This association would take the narrative beyond just the use of antiangiogenic therapy as adjuvant. Available evidence from randomized phase II testing of bevacizumab and atezolizumab, as well as avelumab and axitinib, suggests the combination of PD-L1 or

PD-1 inhibition with VEGF/VEGFR inhibition is additive.[13,14] Thus, potentially, VEGF/VEGFR inhibition could increase PD-L1 expression in tumors or otherwise prime tumors for PD-1/PD-L1 inhibition. It is worth noting that the 16-gene signature assay of the samples from the S-TRAC trial indicated an association between lower expression of immune response and vascular normalization

genes with higher risk of disease recurrence, with the strongest effects observed in the placebo arm.[15]

PROTECT: Evidence Suggestive of a Relationship Between Outcomes and Dose Intensity

One of the unresolved issues from the ASSURE and S-TRAC trials remains the importance of dose intensity and whether maintaining it can result in an improvement in DFS. The PROTECT study pursued this avenue as it provided more data on the relationship between dose and benefit and whether adjustments in exposure to pazopanib could have a significant impact. The PROTECT study evaluated the efficacy of pazopanib as an adjuvant therapy for patients with locally advanced RCC at a high risk of relapse after surgery. The primary objective of the study had to be amended to examine DFS in a cohort that received a reduced dose of pazopanib (600 mg daily instead of the initial 800 mg) due to toxicity.[16] In the 600 mg cohort, a DFS benefit for pazopanib over placebo was not observed. Although a DFS benefit was observed in the sustained 800 mg cohort, it was not considered tolerable. Sun et al introduce the intriguing concept of whether the potential benefit of adjuvant therapy is not completely driven by the starting dose of the drug but rather by blood concentration levels.

This was the focus of another recent report by Sternberg et al[17] who evaluated the relationship between pazopanib exposure (C_{trough}) and efficacy and safety. One of the issues elucidated in this report is whether higher pazopanib exposure as indicated by C_{trough} values could improve DFS without increasing treatment discontinuations of grade 3 and 4 AEs. Sternberg et al found that higher pazopanib exposure was associated with an improved DFS without an increase in the AEs. The analysis also reviewed pharmacokinetic simulations showing overlapping pazopanib exposure with 600 and 800 mg doses. Therefore, some patients achieve higher pazopanib exposure—associated with improved DFS—regardless of whether the starting dose is 600 or 800 mg. Clearly, further study is needed to delineate to what extent the potential benefit of adjuvant therapy is driven by a pharmacokinetic benefit rather than by dose. An additional issue up for debate is whether the results from this study could be extrapolated to sunitinib and other VEGFR receptor TKIs. If the controversy over adjuvant therapy needed yet another focus to stimulate debate, then the challenge has been issued.

Pooled Analysis, a Fourth Trial of Targeted Therapy and Future Directions

Skeptics of S-TRAC can also point to another report by Sun et al[16] who took a different approach to examining the data with a pooled analysis from ASSURE, S-TRAC and PROTECT. This analysis, based on eight articles and five studies of the three trials, revealed:

- No statistically significant effect between adjuvant VEGFR-targeted therapy and improved DFS or OS in patients with intermediate/high risk local or regional fully resected RCC.
- No evidence that dose intensity could significantly improve DFS. Any effect on DFS, they suggest, could be too costly in terms of the toxicity experienced by a majority of patients.

In April of 2018, Pfizer announced by press release that the independent data monitoring committee for the Phase III ATLAS trial (randomized to adjuvant axitinib for up to 3 years vs placebo, NCT01599754) recommended stopping the trial at a planned interim analysis due to futility.[18] This represented the fourth trial of adjuvant therapy with a targeted therapy agent and the third to suggest no benefit. However, the full results have not been presented at a scientific congress, nor have they been published; they are eagerly awaited. Three other ongoing randomized clinical trials are evaluating the clinical benefit of adjuvant targeted therapies, including SORCE (adjuvant sorafenib vs placebo, NCT00492258), EVEREST (adjuvant everolimus vs placebo, NCT01120249), and E2810 (adjuvant pazopanib vs placebo in patients with no evidence of disease following metastasectomy, NCT01575548) (10).

Currently, there are several trials evaluating anti-PD-1 or anti-PD-L1 antibodies in the adjuvant setting: CheckMate 914 (combination of nivolumab and ipilimumab vs placebo), PROSPER (nivolumab neoadjuvantly for 2 doses then adjuvantly vs immediate nephrectomy then observation), IMmotion 010 (atezolizumab vs placebo), and KeyNote 564 (pembrolizumab vs placebo) (ClinicalTrials.gov: NCT03138512, NCT03024996, NCT03142334, NCT03055013). However, there are no combination adjuvant studies of VEGF/VEGFR inhibition with PD-1 or PD-L1 inhibition. The available data would support such an approach in the adjuvant setting.

Conclusion

The landscape of adjuvant therapy remains unsettled and many issues need to be resolved before a consensus can be reached. Four pivotal trials, ASSURE, S-TRAC, PROTECT and ATLAS, have provided discordant results as to whether antiangiogenic therapy in the setting of locoregional RCC can meet the endpoint of DFS. The question of OS is also unresolved. The focus of the initial debate, in large part related to selection of the high risk cohort, dose intensity, independent radiographic review for the DFS endpoint, histology, and independent pathologic review of histology, has shifted as new reports highlight the potential importance of biomarkers and pharmacokinetic factors in determining the optimal approach. Maintaining high-dose intensity has been the tenet of the pivotal trials but it may no longer be the most important question to be addressed. Ongoing trials, including the examination of immune checkpoint inhibitor immunotherapies, will need to address many of these concerns as a consensus remains elusive.

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xenograft) RNA-sequencing data, an empirical approach, DisHet, was able to dissect the tumor microenvironment (eTME). Using eTME, genomics, pathology, and medical record data involving >1,000 patients, the study established an inflamed pan-RCC subtype (IS) enriched for regulatory T cells, natural killer cells, TH1 cells, neutrophils, macrophages, B cells, and CD8+ T cells. IS is enriched for aggressive RCCs, including BAP1-deficient clear-cell and type 2 papillary tumors. The IS subtype correlated with systemic manifestations of inflammation such as thrombocytosis and anemia, which are enigmatic predictors of poor prognosis. Furthermore, IS was a strong predictor of poor survival. The analyses suggest that tumor cells drive the stromal immune response. These data provide a missing link between tumor cells, the TME, and systemic factors.
Conclusion: the authors undertook a novel empirical approach to dissect the RCC TME by leveraging tumorgrafts. The dissection and downstream analyses uncovered missing links between tumor cells, the TME, systemic manifestations of inflammation, and poor prognosis.

The classification of pediatric and young adult renal cell carcinomas registered on the children's oncology group (COG) protocol AREN03B2 after focused genetic testing. Cajaiba MM, Dyer LM, Geller JI, et al. *Cancer.* 2018 Aug;124(16):3381-3389.
Summary: Renal cell carcinomas (RCCs) are rare in young patients. Knowledge of their pathologic and molecular spectrum remains limited, and no prospective studies have been performed to date in this population. This study analyzed patients diagnosed with RCC who were prospectively enrolled in the AREN03B2 Children's Oncology Group (COG). The objective was to classify these tumors with the aid of focused genetic testing and to characterize their features. All tumors registered as RCC by central review were retrospectively re-reviewed and underwent additional ancillary studies. Tumors were classified according to the 2016 World Health Organization classification system when possible. In total, 212 tumors were identified, and these were classified as microphthalmia transcription factor (MiT) translocation RCC (MiT-RCC) (41.5%), papillary RCC (16.5%), renal medullary carcinoma (12.3%), chromophobe RCC (6.6%), clear cell RCC (3.3%), fumarate hydratase-deficient RCC (1.4%), and succinate dehydrogenase-deficient RCC (0.5%). Other subtypes included tuberous sclerosis-associated RCC (4.2%), anaplastic lymphoma kinase (ALK)-rearranged RCC (3.8%), thyroid-like RCC (1.4%), myoepithelial carcinoma (0.9%), and unclassified (7.5%). MiT-RCCs were classified as either transcription factor E3 (TFE3) (93.2%) or EB (TFEB) (6.8%) translocations, and characterization of fusion partners was possible in most tumors.
Conclusion: The current study delineates the frequency of distinct RCC subtypes in a large prospective series of young patients and contributes knowledge to the diagnostic, clinical, and genetic features of MiT-RCC, the most common subtype among this age group. The identification of rare subtypes expands the spectrum of RCC in young patients, supporting the need for a thorough diagnostic workup. These studies may aid in the introduction of specific therapies for different RCC subtypes in the future.

Prevalence of germline mutations in cancer susceptibility genes in patients with advanced renal cell carcinoma. Carlo MI, Mukherjee S, Mandelker D, et al. *JAMA Oncol.* 2018 Sep 1;4(9):1228-1235.
Summary: The prevalence of cancer-related germline mutations in patients with advanced RCC and the phenotypes associated with some rare mutations are unknown. This study examined the prevalence of germline mutations in both known RCC predisposition genes and other cancer-associated genes and to identify clinical and pathologic factors associated with germline mutations. In this 2-year cohort study, 254 of 267 patients with advanced (American Joint Committee on Cancer stage III or IV) RCC who were seen in medical oncology or urology clinics agreed to germline sequencing and disclosure of results. Mutation prevalence and spectrum in patients with advanced RCC were determined. Clinical characteristics were assessed by mutation status. Of the 254 patients (median age [range], 56 [13-79] years; 179 [70.5%] male; 211 [83.1%] non-Hispanic white), germline mutations were identified in 41 (16.1%); 14 (5.5%) had mutations in syndromic RCC-associated genes (7 in FH, 3 in BAP1, and 1 each in VHL, MET, SDHA, and SDHB). The most frequent mutations were CHEK2 (n=9) and FH (n=7). Of genes not previously associated with RCC risk, CHEK2 was overrepresented in patients compared with the general population, with an odds ratio of RCC of 3.0 (P=.003). Patients with non-clear cell RCC were significantly more likely to have an RCC-associated gene mutation (9 [11.7%] of 74 vs 3 [1.7%] of 177), and 8 (10.0%) had a mutation in a gene that could guide therapy. Of patients with mutations in RCC-associated genes, 5 (35.7%) failed to meet current clinical guidelines for genetic testing.
Conclusion: Of patients with non-clear cell RCC, more than 20% had a germline mutation, of which half had the potential to direct systemic therapy. Current referral criteria for genetic testing did not identify a substantial portion of patients with mutations, supporting the role of a more inclusive sequencing approach.

KIM-1 as a blood-based marker for early detection of kidney cancer: a prospective nested case-control study. Scelo G, Muller DC, Riboli E, et al. *Clin Cancer Res.* 2018 Jul 23. doi: 10.1158/1078-0432.CCR-18-1496.
Summary: Kidney injury molecule-1 (KIM-1) has been shown to be elevated in the plasma of RCC patients. This study tested whether plasma KIM-1 could represent a means of detecting RCC prior to clinical diagnosis. KIM-1 concentrations were measured in prediagnostic plasma from 190 RCC cases and 190 controls nested within a

population-based prospective cohort study. Cases had entered the cohort up to 5 years before diagnosis, and controls were matched on cases for date of birth, date at blood donation, sex, and country. The incidence rate ratio (IRR) of RCC for a doubling in KIM-1 concentration was 1.71, corresponding to an IRR of 63.3, comparing the 80th to the 20th percentiles of the KIM-1 distribution in this sample. Compared with a risk model including known risk factors of RCC (age, sex, country, body mass index, and tobacco smoking status), a risk model additionally including KIM-1 substantially improved discrimination between cases and controls. High plasma KIM-1 concentrations were also associated with poorer survival.
Conclusion: Plasma KIM-1 concentrations could predict RCC incidence up to 5 years prior to diagnosis and were associated with poorer survival. KCJ

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ipated in 2018 for the pivotal TIVO-3 trial, a randomized, controlled, multicenter, open-label study comparing tivozanib to sorafenib in patients with refractory advanced RCC.

Natera and Fox Chase Cancer Center to collaborate on kidney cancer study

SAN CARLOS, CA—Natera, Inc. has partnered with Fox Chase Cancer Center to assess the company's Signatera™ (Research-Use Only) customized circulating tumor DNA (ctDNA) assay for recurrence monitoring of kidney cancer. The study will analyze biological specimens collected and banked from 49 patients diagnosed with kidney cancer—including a group whose cancer recurred and a group that did not recur after three years or more. The study will use Natera's proprietary customized assay and next-generation sequencing (NGS)-based technology to determine whether Signatera (RUO) can be used to distinguish between the recurring and non-recurring kidney cancer cases. The study will be led by Philip Abbosh, MD, PhD, assistant professor, Molecular Therapeutics Program, Fox Chase Cancer Center.

"There is a paucity of data for circulating tumor DNA in kidney cancer. This research study will explore a novel approach for disease recurrence and treatment response monitoring in kidney cancer, since existing methods have limitations with sensitivity and specificity," Dr Abbosh said. "Determining the relationship between kidney cancer genetic profiles and prognosis including recurrence using the Signatera assay has great potential to improve patient care by detecting cancer recurrence earlier, assisting adjuvant therapy decision-making, determining treatment effects, and assessing the need for intervention during follow-up."

Discovery of kidney cancer driver could lead to new treatment strategy

CHAPEL HILL, North Carolina — University of North Carolina Lineberger Comprehensive Cancer Center scientists have uncovered a potential therapeutic target for kidney cancers that have a common genetic change. Scientists have known this genetic change can lead to an overabundance of blood vessels, which help feed nutrients to the tumors. Their latest finding shows a potential new cancer-driving pathway.

More than 90% of the most common type of kidney cancer have a genetic change that leads to the loss of an important tumor suppressor gene called VHL. In a study published in the journal *Science*, researchers identified a new downstream effect of this genetic change that is helping to drive kidney cancer: They found that a protein called ZHX2 over-accumulates in these cells and helps to turn on other signals involved in cancerous growth. Their findings suggest that ZHX2 is a potential new therapeutic target for clear cell RCC.

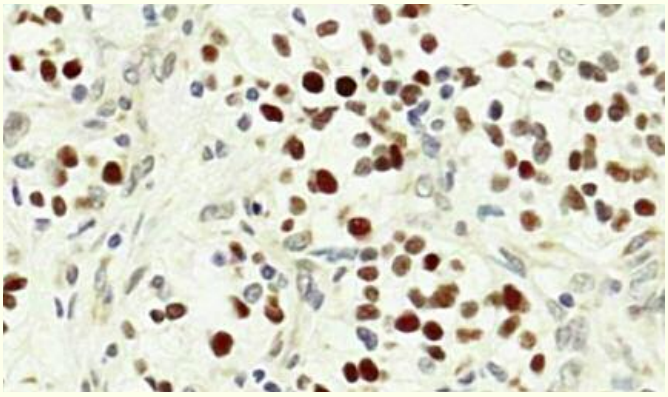

Image shows clear cell renal cell carcinoma with ZHX2 highlighted in brown. *Credit: Jing Zhang, PhD*

Targeted therpies block cell signals involved in abnormal blood vessel production — which is a downstream effect of VHL loss — that are part of the standard of care. Patients can show little response to these drugs or can develop resistance, so Zhang and his colleagues wanted to search for other targets that accumulate in cells lacking VHL function that help to drive the abnormal cancerous growth.The researchers created a screening technique to discover new molecules that might help drive cancer when VHL is lost. This led them to determine that kidney cancer cells lacking VHL usually had more ZHX2. By eliminating ZHX2 from their laboratory models, they inhibited cancer cell growth, invasion and the cancer's spread. In addition, they saw that it was involved with signals that can help cancer cells grow. KCJ

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333 E. 75th Street, Suite 5D
New York, NY 10021.