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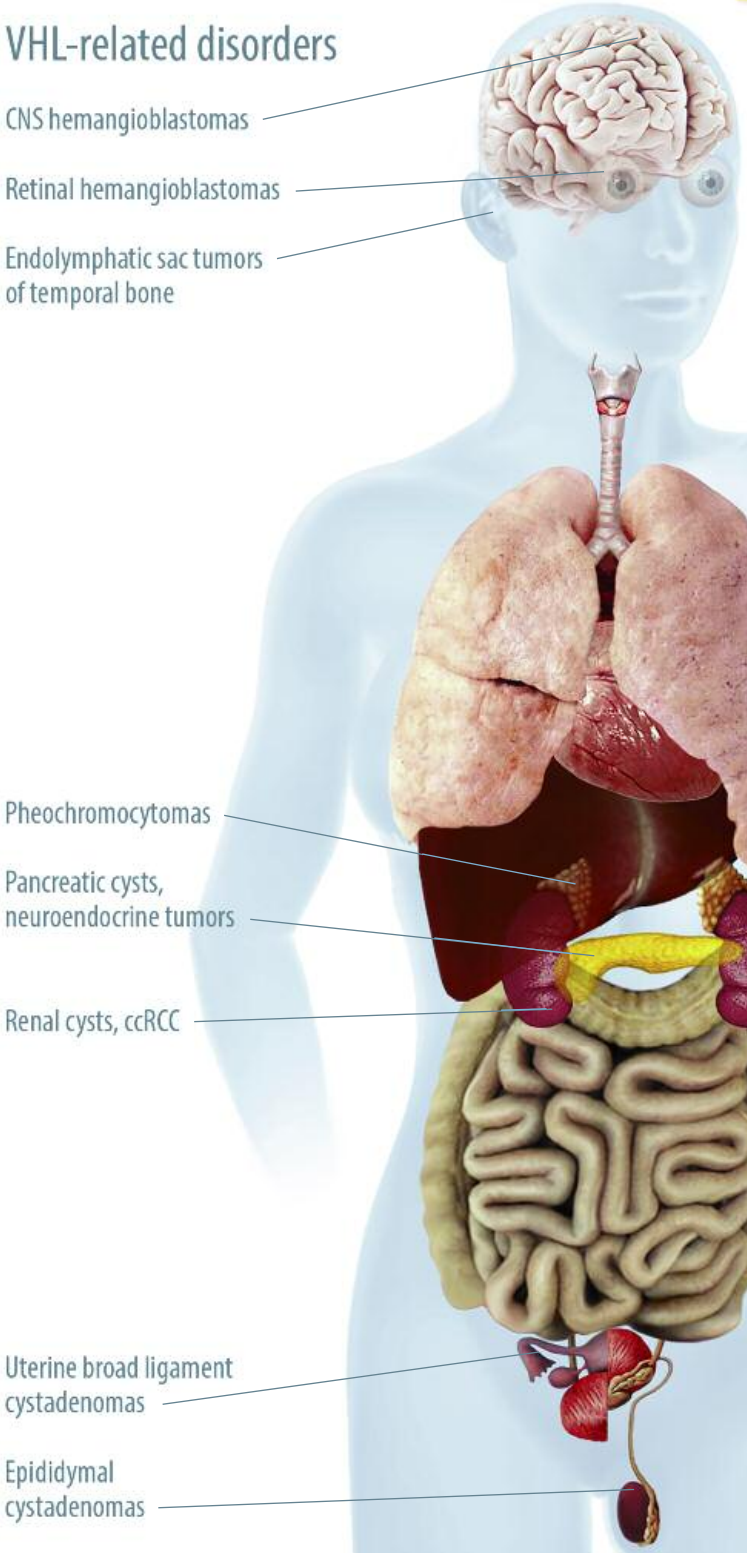

Why the VHL Connection Holds Key to Downstream Targets

Also:

Non-Clear Cell RCC: An Ultimate Guide to Classification and Treatment

New Data on Late Relapsing RCC Clarifies Prognosis

Guidelines for Evaluation

- Annual ophthalmologic exam
- Annual plasma metanephrine, normetanephrine, chromogranin
- Annual abdominal imaging
- Annual audiometry
- MRI of CNS Q2 y

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

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

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About the Cover
Illustration depicts clinical manifestations of von Hippel-Lindau (VHL) disease. Affected persons are at risk for tumor development in the CNS, pancreas, adrenal gland, kidney, and reproductive system. Recommended periodic evaluations are also indicated. (Image courtesy of Thai H. Ho, MD)

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KCJ GUEST EDITOR'S MEMO

Take-Home Message on Treatment Choices: Drill Down Into the Data to Find the "Devil in the Details"


Roberto Pili, MD

When oncologists gather in late April at the 17th International Kidney Cancer Symposium (IKCS) in Prague, they will be exploring a myriad of investigative directions, options for therapy, and cutting edge concepts, in many cases, picking up on themes featured at the recent GU ASCO meeting in San Francisco. If there was one consistent theme emerging from GU ASCO—one that has long stood at the center of the narrative on treating renal cell carcinoma (RCC)—it is the need to identify predictive biomarkers to help us determine optimal sequential and combinatorial therapies. This is often referred to as the "holy grail" of our quest for optimizing outcomes and although expectations remain high for such a discovery, the reality sets in and we know validating such biomarkers is still daunting.

Nevertheless, this will only serve to again fuel the vigorous debate that will challenge attendees at the IKCS, sponsored by the Kidney Cancer Association. Until these reliable biomarkers emerge, we need to direct much of our attention to the nuances in treatment approaches covered at GU ASCO. In that sense, I suggest we get beyond the excitement generated by recent approvals and assiduously drill down into the data to find the "devil in the details", so to speak. And one does not need look very far. By that I mean consider all of the cautionary tales that surround the proposed "treatment paradigms" for first line and second line therapies. This is not to diminish what has been proposed by groups like the National Comprehensive Cancer Network (NCCN). It's more a question of remaining mindful—and vigilant—of those details often overlooked when applying the data to clinical practice.

There are numerous examples of such settings. For example, consider the implications from the 2017 ESMO conference where data from CheckMate-214 emerged. If one were to unqualifiedly accept the findings without drilling down into the data, as proposed earlier, should all patients receive the combination of nivolumab and ipilimumab over sunitinib? As an Editorial in ASCO's daily news summary suggested, unique patient-related characteristics provide a rationale for choosing one agent, or a combination of agents, over another. With due diligence, you would consider the criteria

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Kidney Cancer Journal Author Guidelines

Scope of Manuscripts

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

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

Manuscript Submission

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

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

Peer Review and Editing

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

Conflict of Interest

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

Manuscript Preparation

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

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

References

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

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Essential Peer-Reviewed Reading in Kidney Cancer

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

Quality of life outcomes for cabozantinib versus everolimus in patients with metastatic renal cell carcinoma: METEOR phase III randomized trial. Cella D, Escudier B, Tannir NM, et al. *J Clin Oncol*. 2018 Mar 10;36(8):757-764.
Summary: In the phase III METEOR trial, 658 previously treated patients with advanced renal cell carcinoma were randomly assigned 1:1 to receive cabozantinib or everolimus. The cabozantinib arm had improved progression-free survival, overall survival, and objective response rate compared with everolimus. Changes in quality of life (QoL), an exploratory end point, are reported here. Patients completed functional assessment questionnaires. Data were summarized descriptively and by repeated-measures analysis (for which a clinically relevant difference was an effect size ≥ 0.3). Time to deterioration (TTD) was defined as the earlier of date of death, radiographic progressive disease, or ≥ 4-point decrease from There was no difference over time in data gathered between the cabozantinib and everolimus arms. Cabozantinib improved TTD overall, with a marked improvement in patients with bone metastases at baseline.
Conclusion: In patients with advanced RCC, relative to everolimus, cabozantinib generally maintained QoL to a similar extent. Compared with everolimus, cabozantinib extended TTD overall and markedly improved TTD in patients with bone metastases.

Cabozantinib, a new standard of care for patients with advanced renal cell carcinoma and bone metastases? Subgroup analysis of the METEOR Trial. Escudier B, Powles T, Motzer RJ, et al. *J Clin Oncol.* 2018 Mar 10;36(8):765-772.
Summary: Six hundred fifty-eight patients were randomly assigned 1:1 to receive 60 mg cabozantinib or 10 mg everolimus. Prespecified subgroup analyses of PFS, OS, and ORR were conducted in patients grouped by baseline bone metastases status per independent radiology committee (IRC). Additional end points included bone scan response per IRC, skeletal-related events, and changes in bone biomarkers. For patients with bone metastases at baseline (cabozantinib [n = 77]; everolimus [n = 65]), median PFS was 7.4 months for cabozantinib versus 2.7 months for everolimus. Median OS was also longer with cabozantinib (20.1 months v 12.1 months), and ORR per IRC was higher (17% v 0%). The rate of skeletal-related events was 23% with cabozantinib and 29% with everolimus, and bone scan response per IRC was 20% versus 10%, respectively. PFS, OS, and ORR were also improved with cabozantinib in patients without bone metastases. Changes in bone biomarkers were greater with cabozantinib than with everolimus. The overall safety profiles of cabozantinib and everolimus in patients with bone metastases were consistent with those observed in patients without bone metastases.
Conclusion: Cabozantinib treatment was associated with improved PFS, OS, and ORR when compared with everolimus treatment in patients with advanced RCC and bone metastases and represents a good treatment option for these patients.

Pooled analysis of stereotactic ablative radiotherapy for primary renal cell carcinoma: A report from the International Radiosurgery Oncology Consortium for Kidney (IROCK). Siva S, Louie AV, Warner A, et al. *Cancer.* 2018 Mar 1;124(5):934-942.
Summary: Individual patient data sets from 9 International Radiosurgery Oncology Consortium for Kidney institutions across Germany, Australia, the United States, Canada, and Japan were pooled. Of 223 patients, 118 received single-fraction SABR, and 105 received multifraction SABR. The mean patient age was 72 years, and 69.5% of patients were men. There were 83 patients with grade 1 and 2 toxicity (35.6%) and 3 with grade 3 and 4 toxicities (1.3%). The rates of local control, cancer-specific survival, and progression-free survival were 97.8%, 95.7%, and 77.4%, respectively, at 2 years; and they were 97.8%, 91.9%, and 65.4%, respectively, at 4 years. Tumors with a larger maximum dimension and the receipt of multifraction SABR were associated with poorer progression-free survival (hazard ratio, 1.16 [$P < .01$] and 1.13 [$P = .02$], respectively) and poorer cancer-specific survival (hazard ratio, 1.28 [$P < .01$] and 1.33 [$P = .01$], respectively). There were no differences in local failure between the single-fraction cohort (n = 1) and the multifraction cohort (n = 2; $P = .60$).
Conclusion: SABR is well tolerated and locally effective for treating patients who have primary renal cell carcinoma and has an acceptable impact on renal function. An interesting observation is that patients who receive single-fraction SABR appear to be less likely to progress distantly or to die of cancer.

Axitinib in combination with pembrolizumab in patients with advanced renal cell cancer: a non-randomised, open-label, dose-finding, and dose-expansion phase 1b trial. Atkins MB, Plimack ER, Puzanov I, et al. *Lancet Oncol.* 2018 Mar;19(3):405-415.

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

GU ASCO 2018 Report and Highlights

New information on combination therapies dominated the agenda at this year's GU ASCO Symposium as cliical trials further evaluatedwhether the use of these approaches have potential benefit in a frontline setting.

Axitinib + Pembrolizumab Is Tolerable, Exhibits Promising Antitumor Activity in Treatment-Naïve Patients With Advanced RCC

SAN FRANCISCO—Axitinib with pembrolizumab has been shown to be tolerable and to exhibit promising antitumor activity in treatment-naïve patients with advanced renal cell carcinoma (RCC).

This outcome of an ongoing open-label phase Ib study was reported at the 2018 American Society of Clinical Oncology (ASCO) Genitourinary Cancers Symposium. Michael B. Atkins, MD, of Georgetown University Lombardi Comprehensive Cancer Center, explained that prior studies of programmed death-1 (PD-1) checkpoint inhibitors + tyrosine kinase inhibitors of the vascular endothelial growth factor (VEGF) pathway have been characterized by excess toxicity, precluding further development. Dr Atkins and colleagues hypothesized that axitinib, a more selective VEGF-pathway inhibitor, + pembrolizumab (anti-PD-1) would be well tolerated and yield antitumor activity in treatment-naïve patients with advanced RCC.

The phase Ib trial was composed of a dose-finding phase to determine the maximum tolerated dose and dose expansion phase. Axitinib 5 mg was administered orally twice daily with pembrolizumab 2 mg per kg of body weight intravenously every 3 weeks. Tumors were assessed using Response Evaluation Criteria in Solid Tumors v1.1 at baseline, week 12, and every 6 weeks thereafter. The primary endpoint was dose-limiting toxicity during the first 2 cycles (6 weeks). Secondary endpoints evaluated safety, objective response rate, progression-free survival, and overall survival.

No unexpected toxicities were observed. A total of 3 dose-limiting toxicities were reported among the 11 patients treated in the dose-finding phase. A transient ischemic attack was reported in 1 patient and 2 patients received <75% of the planned axitinib dosage due to treatment-related toxicity. At the cut-off date in 2017, 25 patients were receiving study treatment. The most common (at least 10%) grade ≥3 all-causality adverse events included hypertension (23%), diarrhea (10%), and fatigue (10%). The most common (>10%) potentially immune-related adverse events included diarrhea (29%), increased alanine aminotransferase (17%), and aspartate aminotransferase (13%), hypothyroidism (13%), and fatigue (12%).

The objective response rate was 73.1% . Median progression-free survival was 20.9 months. Overall survival data were not mature after the minimum follow-up period of 17.6 months, and 6 treatment-unrelated deaths were reported. Dr Atkins concluded that the combination of axitinib + pembrolizumab was shown to be tolerable and to exhibit promising antitumor activity in treatment-naïve patients with advanced RCC. A randomized phase III comparison of axitinib + pembrolizumab vs sunitinib monotherapy is underway.

An Inflammation Scoring Tool Predicts Overall Survival in Localized Clear Cell RCC

A high-risk clear cell RCC inflammatory score has been shown to be an independent and significant predictor of overall survival, with comparable accuracy to accepted prognostic tools.

This outcome of a retrospective validation study was reported at the 2018 ASCO Genitourinary Cancers Symposium.

Kevin Richard Melnick, DO, of Emory University School of Medicine, explained that a previously created and analyzed composite RCC inflammatory score composed of preoperative serum markers was found to be a significant and independent predictor of overall survival in RCC, with accuracy at least as good as other established prognostic tools. Dr Melnick and colleagues set out to validate the prognostic significance of this novel score in a new, independent cohort of patients with localized clear cell RCC. The new cohort was randomly selected from a group of patients with localized clear cell RCC, who underwent nephrectomy from 2007 to 2017. Data for the group was contained in the investigators' nephrectomy database.

Biomarker composition, cut-offs, and calculations of the RCC inflammatory score were recreated accurately from the previous publication. The final score was the sum of points accrued for each biomarker, ranging from 0 - 10, followed by stratification into baseline (0), low (1 - 3), intermediate (4 - 6), and high-risk (7 - 10) groups. Receiver-operating characteristics and chi-square analysis were performed to compare the prognostic ability of this novel score vs the Stage, SIze, Grade, and Necrosis (SSIGN), UCLA Integrated Scoring System (UISS), modified Glasgow Prognostic Score (mGPS, and Leibovich scores. The impact on overall survival was analyzed using multivariate logistic regression analysis.

IMotion 150: Atezolizumab Plus Bevacizumab Shows Potential

Results from the phase II IMmotion150 study that compared atezolizumab (Tecentriq) plus bevacizumab (Avastin) and atezolizumab monotherapy to sunitinib (Sutent) alone in patients with previously untreated, locally advanced or metastatic RCC were also presented the GU ASCO meeting.

(continued on page 31)

Revisiting the *VHL* Connection: How a Common Pathway Now More Closely Links Sporadic RCC, *VHL*-Associated Syndromes

Eric Jonasch, MD
Professor, Department of
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Division of Cancer Medicine
The University of Texas
MD Anderson Cancer Center
Houston, Texas

The trajectory of recent work on the pathophysiology of renal cell carcinoma (RCC) suggests the extent to which a spectrum of disorders share a common genetic framework. Although the implications of losing the von Hippel-Lindau (VHL) gene have been clear for a long time, an improved understanding of its precise role in tumorigenesis is now emerging. The challenge now is to take these new findings and extrapolate them to treatment choices as we seek to optimize clinical outcomes, not only in RCC but in VHL-related diseases.

A growing awareness of the interaction between germline mutations and somatic tumor mutations has focused more attention on how distinct phenotypes could provide important new information with implications for earlier diagnosis and potential management strategies in hereditary and sporadic renal cell carcinoma (RCC). Advances in genome-wide sequencing technologies have helped move the discourse beyond core driver mutations, including the *VHL* gene, to include additional mutations that affect diverse elements of cellular biology, including chromatin homeostasis. Armed with new data emerging over the last few years, clinicians may have more effective strategies to meet diagnostic, surveillance, and therapeutic challenges in sporadic RCC and in hereditary *VHL* disease.

Although *VHL* disease is rare—occurring in roughly 1 in 36,000 births[1]- this syndrome could yield new clues regarding the molecular pathogenesis of sporadic RCC and could serve as a framework for the application of targeted therapies. As more of the biology of *VHL* disease has unraveled, the implications for potential therapeutic approaches, including the use of antiangiogenic agents and immunotherapy, suggest that we may have more effective ways to have an impact on downstream targets in RCC.

One of the major themes to emerge from newly published work on *VHL* disease is the extent to which hereditary and sporadic RCC share common features regarding their molecular pathogenesis. These include dysregulation of the *VHL* tumor suppressor protein/hypoxia inducible factor axis, ciliogenesis and aberrant tumor metabolism.[2] As the knowledge base for all genetic RCC syndromes expands, the focus is also shifting toward the de-

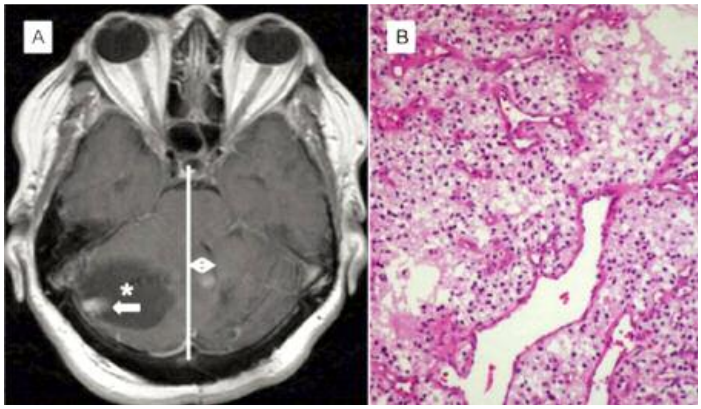

Figure 1. (A) Axial T1 postcontrast images demonstrate an enhancing mural nodule (white arrow) with accompanying cyst (*) in the right cerebellar hemisphere exerting a mass effect upon the midline and fourth ventricle (double white arrow). (B) Hematoxylin-eosin staining showing scattered large hyperchromatic nuclei, vacuolated cells, and multiple capillaries which are classic features of the cellular type of hemangioblastoma. From: Varshney N, Kebede AA, Owusu-Dapaah H, et al. A review of von-Hippel-Lindau syndrome. *J Kidney Cancer VHL*. 2017;4:20-29.

Keywords: von Hippel Lindau (VHL) disease; syndrome; hereditary, genetic mutation; hemangioblastoma; retinal; hypoxia inducible factor; VEGF.

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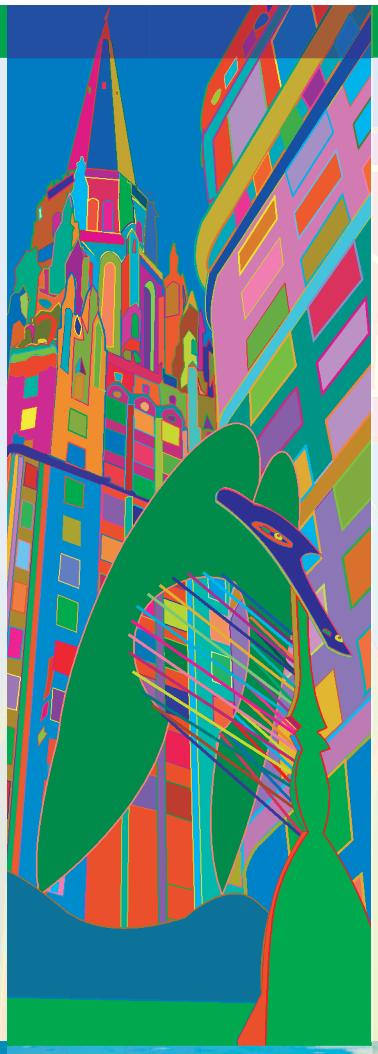

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KCJ INTERVIEW

Encapsulating *VHL* Disease and Seeking to Optimize Outcomes

In this brief interview, Eric Jonasch, MD, offers a perspective on some of the key issues related to von Hippel-Lindau (VHL) disease and the prospects for noninvasive approaches to treatment.

Q. If a patient has been identified with VHL disease, how would you characterize their risk for developing renal cell carcinoma (RCC)?

Dr Jonasch: More than 50% of these cases will develop multifocal, bilateral RCC.

Q. What are the implications when a germline mutation in VHL is identified?

Dr Jonasch: The mutation results in a number of manifestations, including hemangioblastomas, pheochromocytomas, pancreatic neuroendocrine tumors and RCC. Patients endure a lifetime of surveillance and invasive procedures.

Q. What are some of the guidelines with respect to intervention?

Dr Jonasch: The standard of care is still surgical intervention, including ablations. Patients with retinal lesions are candidates for laser and other types of ablation. Among the patients with a hemangioblastoma, there are a number of treatment considerations, including the option of surgery for RCC. With regard to management, there is the 3 cm rule. We have found that if RCC are less than 3 cm, they do not have metastatic potential. However, once they have reached 3 cm, we either recommend surgery, cryoablation or radiofrequency ablation to minimize the risk of metastases. Patients may need multiple surgeries throughout their lifetime to keep them out of trouble.

Q.. Please describe the noninvasive approaches to management.

Dr Jonasch: Our knowledge of the VHL gene and its effect on biology has spurred development of antiangiogenic therapy. Bill Kaelin at Dana Farber, for example, and others have unraveled the biology of the VHL protein and led to the knowledge that this is a regulator of hypoxia-inducible factor (HIF) which, in turn, regulates VEGF (vascular endothelial growth factor). And VEGF regulates angiogenesis. So the angiogenesis blocking agents like sunitinib and bevacizumab in this setting basically arose out of the understanding of VHL biology.

Q. Do we have a favorable outlook with these agents?

Dr Jonasch: None of these agents has been FDA-approved for VHL disease. So what we're trying to do is create a path forward for these agents. There are only a handful of centers in the world that are able to do the research, ours at M.D. Anderson being one of them. We've published a number papers on the medical treatment of VHL disease. And yet, it is all investigational. The big question for the future is can we validate an antiangiogenic agent? Sunitinib is too toxic. Pazopanib is better but it has its own issues. A new clinical trial has just been launched testing a novel HIF-blocking agent, PT2977.

Q. How would you encapsulate your goal in this disease?

Dr Jonasch: The bottom line or goal is to use these agents to decrease the number of surgical interventions. But using therapies that are not so toxic that that the prospects are worse than surgery. For example, after 6 months of receiving sunitinib, most patients preferred surgery. I still have close to 10 patients on a trial receiving pazopanib. They like pazopanib because it is better tolerated. And yet, I remain optimistic when I consider some of the patients on study who excellent quality of life while preventing tumor growth. We've really changed the lives of several of these people.

velopment of screening guidelines to identify patients with germline mutations in the absence of secondary clinical manifestations that are at highest risk for potentially lethal disease manifestations. As we learn which elements are necessary to engender early-onset RCC in syndromic patients, it could help identify persons who have an increased risk of developing sporadic RCC.

Understanding *VHL* Disease, its Genetic Underpinnings, and Pathophysiology

Clear cell RCC can be sporadic (>96%) or familial (<4%). Almost all familial clear cell RCCs arise from an inherited mutation in the *VHL* tumor suppressor gene located on chromosome 3p.[3] Patients with VHL disease develop kidney cysts and multiple bilateral clear cell RCC at an average 37 years of age.[4] The second *VHL* allele has been shown to be inactivated by deletion and less commonly

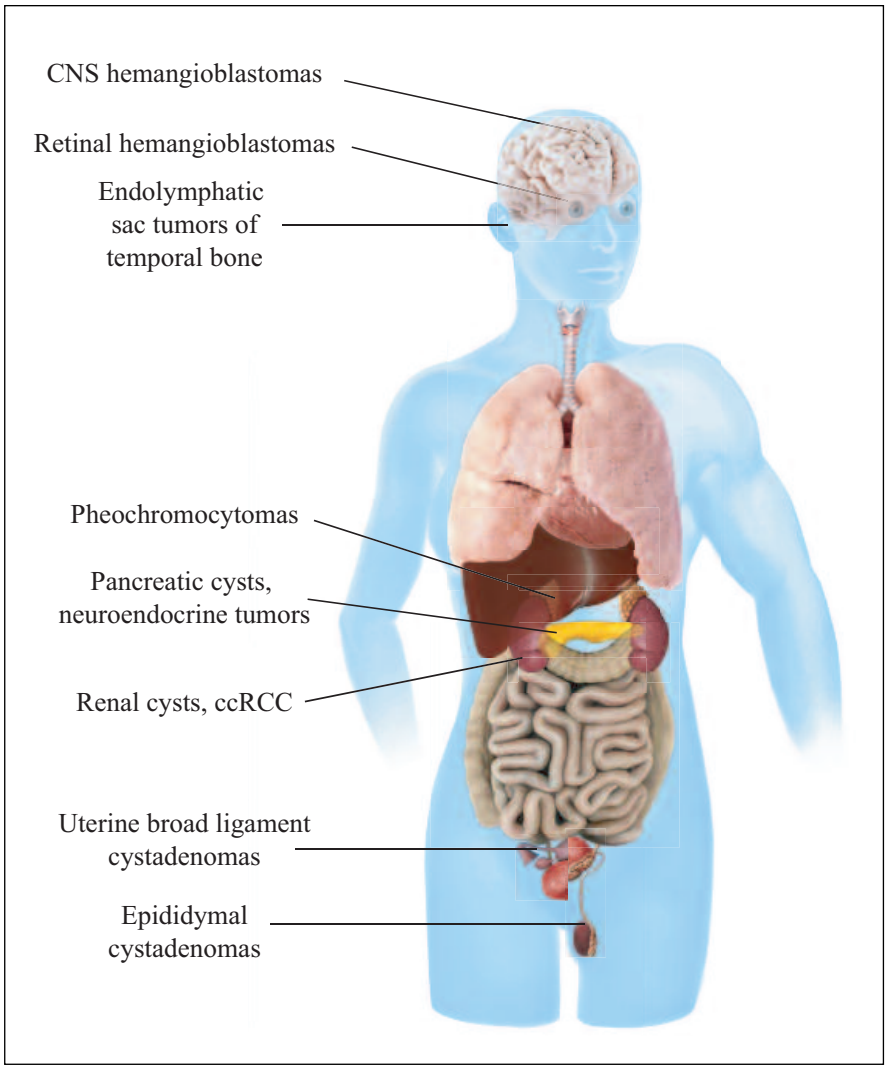

Figure 2. Clinical manifestations of von Hippel-Lindau disease. Sites indicate where an increased risk for tumor development is likely to occur. From: Ho TH, Jonasch E. Genetic kidney cancer syndromes. *J Natl Compr Cancer Netw*; 20144;12:1347-1355.

by promoter hypermethylation or rearrangement. The average age of onset of sporadic clear cell RCC is 61 years and it usually presents as a solitary tumor of several centimeters in size.[4] Chromosome 3p deletion and inactivation of the *VHL* gene is the most common genetic alteration.[5] The fact that *VHL* inactivation is so common in sporadic clear cell RCC, including the smallest T1a tumors, and this is also the predisposing factor in familial *VHL* disease, argues that alteration of *VHL* is the initiating event in most sporadic clear cell RCC.[6]

Recent advances in the understanding of cancer as a genetic disease have allowed the identification of clonal genetic and epigenetic alterations, which accumulate during cancer progression, often in a general temporal order. However, relatively little is known about the secondary and later genetic alterations which drive progression after the initiating event of inactivation of *VHL* in clear cell RCC. Even less is known about the alterations that underlie the initiation and progression of sporadic papillary or chromophobe RCC. It remains that much of what we know of the molecular basis of sporadic RCC arose from identification of the genes predisposing to inherited RCC.[7]

Loss of *VHL* function is associated with several events that can predispose to tumorigenesis. The protein product *VHL* serves as an E3 ubiquitin ligase, and regulates degradation of hypoxia-inducible factors (HIF) under normoxic conditions (1). There are two main HIF transcription factors, HIF-1alpha and HIF-2alpha. Under hypoxic conditions, these HIF isoforms regulate a large number of overlapping and unique target genes, including vascular endothelial growth factor (VEGF).[8,9] This interaction plays a role in cellular adaptation to hypoxia. VEGF is well recognized as an important factor in promoting tumorigenesis. A number of additional VHL functions exist whose loss may also engender tumorigenesis.[10,11]

As outlined below, multiple cancerous and non-cancerous organ-specific manifestations arise in *VHL* patients, with the only known initiating factor being a germline *VHL* mutation. It will be critical to perform cross-lesion analyses to identify the common as well as the discordant features responsible for producing such discrepant phenotypic manifestations.

The Spectrum of Manifestations and Presentations

The clinical manifestations of *VHL* disease include hemangioblastomas, pheochromocytomas, endolymphatic sac tumors, pheochromocytomas, epididymal cystadenomas, pancreatic and renal cysts, pancreatic neuroendocrine tumors and clear cell RCC. The mean age of onset of RCC is 37 years and RCC is the leading cause of death in patients with *VHL* disease. The most common manifestation is CNS hemangioblastoma, (**Fig. 1**) found in 60% to 80% of all *VHL* patients, according to a review by Kim et al.[12] CNS hemangioblastomas can be located anywhere along the neural axis, but most of them are localized in the eye, the cerebellum and the spinal cord (**Fig. 2**). This review will focus primarily on RCC and hemangioblastomas in view of their most common occurrence compared to the other *VHL*-related syndromes, and their relative morbidity.

Treatment: Studies Still Investigational but Antiangiogenic Approaches Look Promising

Since acquired dysregulation of *VHL*-dependent pathways is often apparent in patients with sporadic RCC treated with tyrosine kinase inhibitors (TKIs) the same rationale has been extrapolated for treating *VHL* patients with progressive disease in the kidneys or other sites.[13] This ap-

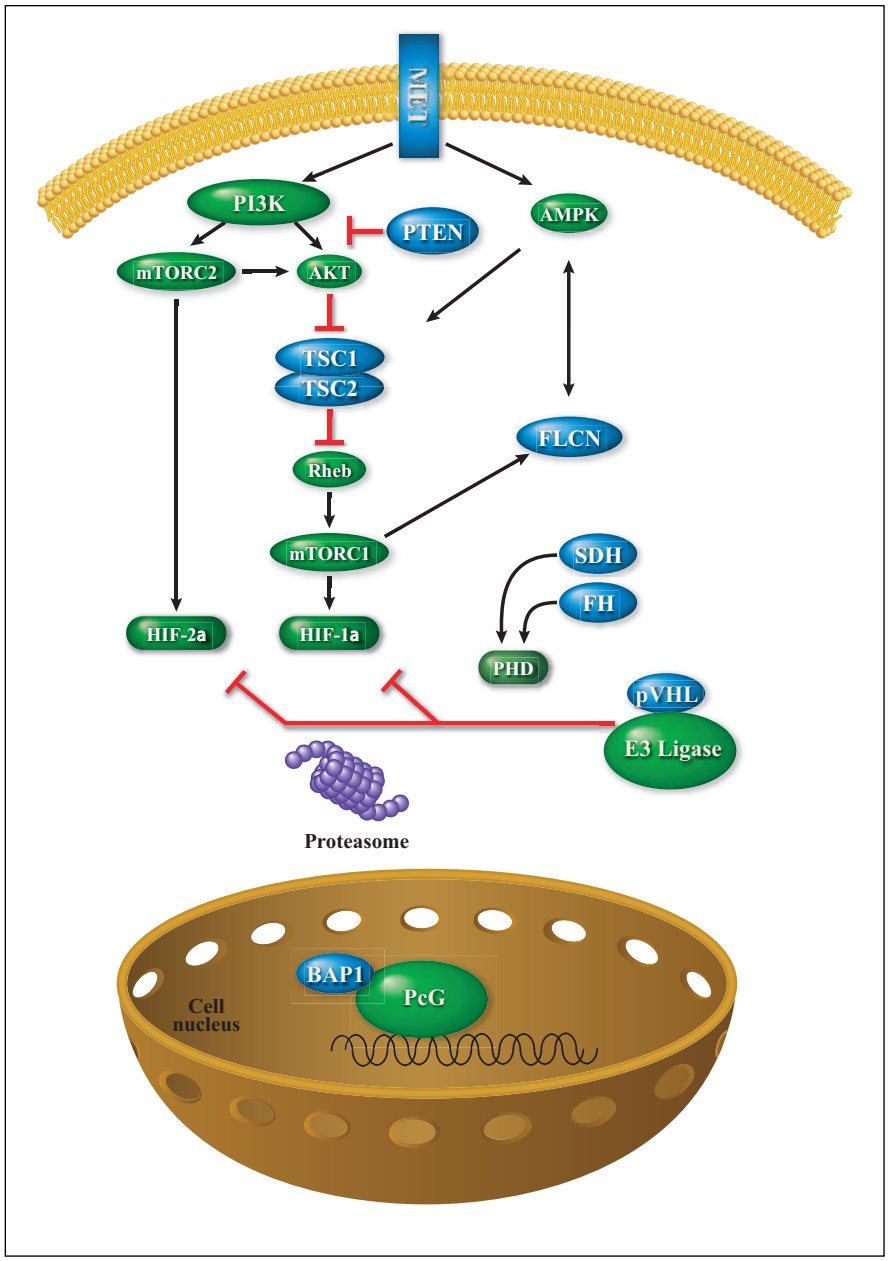

Figure 3. Genes mutated in hereditary kidney cancer syndromes. Mutations (blue) in MET, PTEN, TSC1/TSC2, FLCN, VHL, SDH, FH, and BAP1, are linked to sporadic RCC and hereditary kidney cancer syndromes. VHL mutations play a role in tumorigenesis by affecting hypoxia-inducible factor and cellular adaptation to hypoxia.

proach has been delineated in numerous trials. These reports share a common hypothesis: the most important mechanism involved in the pathogenesis of sporadic and *VHL*-related RCC is the overexpression of angiogenic growth factors stimulated by HIF-1 alpha and HIF-2 alpha after inactivation of *VHL* (**Fig. 3**). Thus, a growing literature has drawn a connection between the treatment of sporadic RCC and the *VHL*-related syndromes. For example, in a landmark paper, Kaelin,[13] suggested that mutations or promoter hypermethylation of the *VHL* gene may be frequently found in sporadic clear cell RCC. It is a logical step then to suggest there may be a correlation with sensitivity to antiangiogenic treatment.

Sunitinib

There are emerging data on the benefit of TKIs in *VHL* disease patients with progressive disease in the kidneys or other sites. The clinical trials have primarily focused on the use of two TKIs, sunitinib and pazopanib; however, other agents have also undergone study such as bevacizumab and ranibizumab. In their retrospective analysis, Roma et al[14] evaluated progression-free survival in 14 patients with genetically-confirmed *VHL* treated for a histological diagnosis of multifocal or advanced RCC. After administering sunitinib as a first systemic treatment, Roma et al recorded 9 partial responses (64.3%) and 5 stabilizations of disease with a PFS of 71.4% at 2 years. All evaluable hemangioblastomas remained stable. More encouraging were the radiological responses observed not only in renal lesions but also in pancreatic, adrenal, hepatic, pulmonary and subcutaneous nodules as well as in some cystic lesions, which represents a wide spectrum of *VHL*-related lesions.

In a prospective trial,[15] we evaluated the safety and efficacy of sunitinib in VHL patients (NCT00330564) and examined the expression of various receptors in archived tissue. Of 18 RCCs, 33% responded favorably although none of the hemangioblastomas did. One intriguing finding concerned the results of biomarker expression: mean levels of VEGF receptors were lower in hemangioblastoma than in RCC and mean fibroblast growth factor receptor (FGFR) activation state was higher in hemangioblastomas. Why do organ-specific *VHL*-derived lesions respond differently to therapy? And what of the findings on fibroblast growth factor (FGF) axis? To what effect does do these differences affect organ specific response rates? At this point in time, we do not have clear answers to these questions, but as previously stated, RCCs are true cancers, whereas hemangioblastomas have no metastatic potential. It could be that the differences are due to cancer-specific genetic lesions or tissue-specific endothelial differences. The results on FGF raise the possibility that further studies should examine whether hemangioblastomas could depend on FGF signaling and whether we can identify biomarkers that will help us determine whether agents will yield some benefit.

Dovitinib

To that end, we launched a phase II study[14] (NCT01-266070) in *VHL* patients to test the hypothesis that hemangioblastomas would respond to dovitinib, which

Tracing the Origins of *VHL* Disease to the Work of Two Physicians

Eugene von Hippel

Arvid Lindau

The investigative work of two physicians began more than 100 years ago, each working independently and unaware of the other's research. Today, the condition they observed bears both of their names, reflecting the discoveries of these two pioneers. They were Eugen von Hippel and Arvid Lindau. When their revelations were further validated, the disease became known as von Hippel-Lindau (VHL) disease.

In 1904, Eugen von Hippel , a German ophthalmologist, described a rare disorder of the retina, and in 1911 discovered the anatomical basis of this disease, which he named "angiomatosis retinae". However, it was not until 1926 that Swedish pathologist Arvid Lindau recognized an association between angiomatosis of the retina with hemangioblastomas of the cerebellum and other parts of the central nervous system. Thus the condition is known today as VHL disease.

Lindau was the first to describe a coherent link between the retinal, cerebellar and visceral components of a disease he called "angiomatosis of the central nervous system". This disease is characterized by tumors of the retina and the brain, along with cysts and tumors of several visceral organs such as the kidneys, pancreas and adrenal glands. Lindau's research soon attracted the attention of famed neurosurgeon Harvey Cushing, who named the disorder, "Lindau's disease". By 1964 the medical community had become more aware of early 20th century research on retinal angiomata conducted by von Hippel, and both men were recognized for their contribution in describing the condition.

blocks FGFR in addition to VEGF receptors. Unfortunately, this study was closed after six patients were enrolled as the toxicity stopping rule was met, mainly because of the development of rash. No responses were observed and this agent was not considered for further development in this indication.

Pazopanib

Efforts to avoid unnecessary surgery for asymptomatic cerebellar hemangioblastomas have also focused on the use of pazopanib. Three case reports have helped provide an avenue for further investigation of this TKI in this setting. The first report from MD Anderson by Kim et al[12] provided evidence demonstrating clinical and radiological anti-tumor response using pazopanib in a patient with treatment-refractory *VHL*-associated CNS hemangioblastoma. Treatment with 800mg/day of pazopanib resulted in significant neurologic improvement and radiologic tumor volume reduction in a 47-year-old African-American male. This case report represented the first time any agent had demonstrated clinical benefit for CNS hemangioblastomas. With the exception of neutropenia, the patient experienced only mild adverse events (grade 1 and 2.)

In a second case report, Swiss authors[17] reported on pazopanib treatment in a 37-year-old female patient with recurrent and rapidly progressive *VHL*-associated hemangioblastomas that caused severe disability. A 24-month treatment with pazopanib achieved progressive improvement in her condition. Radiological findings did not show significant changes in the size of target lesions and did not reveal any new lesion in contrast to the continuous multifocal progression prior to therapy. The report offers further evidence supporting the use of a TKI in this setting and underscoring the rationale of such treatment because RCC harbors the same molecular abnormalities as CNS hemangioblastoma. A third, more recent case report demonstrated heterogeneous response in a patient with multiple CNS hemangioblastomas.[18]

We presented a phase II study testing pazopanib in *VHL* patients (NCT01436227) at the 2017 ASCO meeting.[19] In this trial, 31 *VHL* patients were treated with pazopanib. The objective response rate was 42%, with a greater than 50% response rate in RCCs and in pancreatic lesions. Hemangioblastomas demonstrated a response rate of 4%, but disease stabilization was noted in a number of patients. Two cases of bleeding were reported in hemangioblastomas. This study represents the largest prospective study using an antiangiogenic agent in *VHL* patients, with a number of individuals remaining on study for several years.

Treatment of Retinal Hemangioblastoma

Treatment of retinal hemangioblastomas with intravitreal

or systemic antiangiogenic agents has shown limited success. The hallmark ocular lesion associated with *VHL* disease is the retinal capillary hemangioblastoma, present in about 37% of *VHL* patients.[20] Investigative work, such as the study by Wong et al,[21] used intravitreal ranibizumab a VEGF trapping agent. In the Wong study,[21] five patients received an average of 10 intravitreal injections over an average of 47 weeks. Unfortunately, ranibizumab had minimal beneficial effect on most *VHL*-associated retinal hemangioblastomas, although there was possible efficacy in a patient with the smallest lesion with less exudation. More promising results were achieved in a second study in which bevacizumab was used over 60 months in a patient with progressive visual loss to a *VHL*-associated macular and optic nerve hemangioblastoma.[22] After undergoing a treatment regimen of 15 injections, visual acuity improved 25 letters, ocular coherence thickness improved from 646 um to 4244 um; structural lesions stabilized while exudates and edema resolved. Although the results are somewhat encouraging, it remains to be seen whether localized VEGF blocking therapy with either bevacizumab or ranibizumab will be more than an interim solution.

Novel Treatments for *VHL* disease

The ideal treatment for *VHL* patients would be gene replacement therapy, whereby copies of a normal *VHL* gene can be introduced into patient's cells, thereby normalizing them. At this time, such technology has not yet been developed for patients with *VHL* disease, although the "CRISPR" Cas9 gene editing technology[23] shows promise in an increasingly large number of applications, and could be adapted for this purpose. Short of replacing defective *VHL*, the next best approach would be to block the HIF transcription factor itself. Two HIF2 alpha blocking agents PT2385, and the more recent version PT2977, are in clinical development. PT2385 demonstrated promising results in a recently published phase I clinical trial in patients with advanced malignancies.[24] PT2977 is being tested in a phase I clinical study[25] (NCT02974738) and a second study was launched to test this agent in patients with *VHL* disease[26] (NCT03401788). This latter study holds great promise for patients with *VHL* disease, as HIF blockade would theoretically inhibit development of all *VHL* organ manifestations.

Conclusions

Despite the heterogeneous nature of hereditary and sporadic clear cell RCC, their pathophysiology shares a common dysregulation of the HIF-VEGF axis. The recognition of a shared pathway offers the potential to develop an understanding of the common drivers of tumor progression and lethality in sporadic and hereditary *VHL*-related disease. Although still investigational, ongoing trials using TKIs and HIF-targeted therapy will hopefully provide the compelling data needed to support the use of such therapies in the hereditary *VHL* patient population.

References

1.Ashouri K, Mohseni S, Tourtelot J, et al. Implications of von Hippel-Landau syndrome and renal cell carcinoma. *J Kidney Cancer and VHL*. 2015;2:13-1773.

2. 1. Ho TH, Jonasch E. Genetic kidney cancer syndromes. *J Natl Compr Cancer Netw*. 2014;12:1347-1355.

3. Latif F, Tory K, Gnarra J, et al. Identification of the von Hippel-Lindau disease tumor suppressor gene. *Science*. 1993;260:1317–1320.

4. Pavlovich CP, Schmidt LS, Phillips JL. The genetic basis of renal cell carcinoma. *Urol Clin North Am*. 2003;30:437–454. vii.

5. Gnarra JR, Tory K, Weng Y, et al. Mutations of the *VHL* tumour suppressor gene in renal carcinoma. *Nature Genet*. 1994;7:85–90.

6. Cairns P. Renal cell carcinoma. *Cancer Biomark*. 2011;9:461-473.

7. Linehan WM, Zbar B. Focus on kidney cancer. *Cancer Cell*. 2004;6: 223–228.

8. Cockman ME, Masson N, Mole DR, et al. Hypoxia inducible factor-alpha binding and ubiquitylation by the von Hippel-Lindau tumor suppression protein. *J Biol Chem*. 2000;275:257733-25741.

9. Comprehensive molecular characterization of clear cell renal cell carcinoma. *Nature*. 2013;499:43-49.

10. Jonasch E, Futreal PA, Davis IJ, et al. State of the science: an update on renal cell carcinoma. *Mol Cancer Res*. 2012;10:859-880.

11. Scanlon SE, Hegan DC, Sulkowski PL, et al. Suppression of homology-dependent DNA double-strand break repair induces PARP inhibitor sensitivity in VHL-deficient human renal cell carcinoma. *Oncotarget*. 2017;9:446647-460.

12. Kim BYS, Jonasch E, McCutcheon IE. Pazopanib therapy for cerebellar hemangioblastomas in von Hippel-Lindau disease. Case report. *Targ Oncol*. 2012;7:145-149.

13. Kaelin WG. Treatment of kidney cancer: insights provided by the VHL tumor-suppressor protein. *Cancer*. 2009;115:2262-2272.

14. Roma A, Maruzzo M, Basso U, et al. First-line sunitinib in patients with renal cell carcinoma (RCC) in von Hippel-Lindau (VHL) disease: clinical outcome and patterns of radiological response. *Familial Cancer*. 2015;14:309-3166.

15. Jonasch E, McCutcheon IE, Waguespack SG, et al. Pilot trial of sunitinib therapy in patients with von Hippel-Lindau disease. NCT00330564.

16. A Pilot Trial of TKI 258 (Dovitinib) in Von Hippel-Lindau Syndrome. NCT01266070.

17. Migliorini D, Haller S, Merkler D, et al. Recurrent multiple CNS hemangioblastomas with VHL disease treated with pazopanib: a case report and literature review. *CNS Oncol*. 2015;4:387-392.

18. Taylor DG, Ilyas A, Mehta GU, et al. Variable response of CNS hemangioblastomas to Pazopanib in a single patient with von Hippel-Lindau disease: Case report. *J Clin Neurosci*. 2018;50:154-156.

19. Jonasch E, Gombos DS, Waguespack SG, et al. Phase II study of pazopanib in patients with von Hippel-Lindau disease. Abstract. 2017 ASCO Annual Meeting. NCT0144362277.

20. Wong WT, Agron E, Coleman HR, et al. Genotype-phenotype correlation in von Hippel-Lindau disease with retinal angiomatosis. *Arch Ophthalmol*. 20077;125:239-245.

21. Wong WT, Liang KJ, Hammel K, et al. Intravitreal ranibizumab therapy for retinal capillary hemangioblastoma related to von Hippel-Lindau disease. *Ophthalmol*. 2008;115:1957-1964.

22. Hrisomalos FN, Maturi RK, Pata V. Long-term use of intravitreal bevacizumab (Avastin) for the treatment of von Hippel-Lindau associated retinal hamangioblastomas. *The Open Ophthalmology Journal*. 2010;4:66-69.

23. Gupta RM, Musunuru K. Expanding the genetic editing tool kit: ZFNs, TALENs, and CRISPR-Cas9. *J Clin Invest*. 2014 Oct;124(10):4154-61.

24. Courtney KD, Infante R, Lam ET. Et al. Phase I Dose-Escalation Trial of PT2385, a First-in-Class Hypoxia-Inducible Factor-2 Antagonist in Patients With Previously Treated Advanced Clear Cell Renal Cell Carcinoma. *J Clin Oncol*. 2018;36:867-874.

25. A Phase 1, Multiple-Dose, Dose-Escalation and Expansion Trial of PT2977, a HIF-2 Inhibitor, in Patients With Advanced Solid Tumors. NCT 02974738.

26. Open-Label Phase 2 Study to Evaluate PT2977 for the Treatment of Von Hippel Lindau Disease-Associated Renal Cell Carcinoma. NCT03401788. KCJ

The Classification and Treatment of Non-Clear Cell Renal Cell Carcinoma


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Introduction/Epidemiology

Renal cell carcinoma (RCC) is the 8th most common cancer in the United States with an estimated incidence of 63,990 causing 14,400 deaths in 2017 according to the National Cancer Institute's Surveillance, Epidemiology, and End Result (SEER) program data.[1] From 1975 to 2014, the incidence of RCC increased from 7 to 15 per 100,000 people. This finding is likely due in part to the increased use of imaging studies leading to the detection of small, asymptomatic renal tumors. Recently, Welch and colleagues found that hospital referral regions that utilized computerized tomography (CT) with greater frequency also experienced higher rates of nephrectomy, presumably reflecting the increased rate in detection of incidental renal masses.[2]

Cigarette smoking, increased body mass index (BMI), and high blood pressure are all established risk factors for the development of renal cell carcinoma. Smoking cessation and also possibly treatment of hypertension are associated with a reduction in risk.[3] Increased risk of developing RCC has also been observed in some studies in patients with diabetes mellitus[4], increased parity[5], and in patients with history of trichloroethylene exposure.[6] Conversely, an inverse relationship has been suggested between physical activity and alcohol consumption and the development of RCC. The study of the relationship between diet and RCC has yielded conflicting results with some data suggesting a protective effect from a diet rich in fruits and vegetables and increased risk associated with high fat diets or intake of processed meats.[7] RCC affects males twice as often as females and typically affects older adults with a median age at diagnosis of 64.[8] Higher incidence is found among Blacks, American Indians, Alaska Natives, Whites, and Hispanics as compared to Asians and Pacific Islanders.[9]

Among all malignant renal neoplasms, renal cell carcinoma (RCC) represents 90% of cases.[10] RCC itself is a heterogeneous group of malignant epithelial neoplasms that is further categorized based on histopathologic, genetic features and clinical behavior ranging from indolent to highly aggressive. RCC is primarily comprised of clear cell type, representing about 75%, while non-clear cell RCC represents approximately 25%.[11] Non-clear cell renal carcinomas can be further subdivided into, papillary (10-15%), chromophobe (5%), collecting duct (1%), medullary (<1%), translocation (1-3%), and unclassified (5%) types.[11-12] A clear understanding of the different characteristics of these subtypes of non-clear cell RCC is critical for prognostication and for identification of suitable treatments.

Classification of Non-Clear Cell RCC

Non-clear cell RCC subtypes are classified according to cell of origin, histology, immunohistochemical staining, molecular biology, and tumor genetics (**Table 1**). The main subtypes of non-clear cell RCC include papillary, chromophobe, collecting duct, medullary, translocation, and unclassified. Sarcomatoid features, once thought to

Key Words: Non-clear cell renal cell carcinoma; classification, subtypes, papillary, chromophobe, collecting duct, medullary,translocation, unclassified, treatment, VEGF receptor inhibitor, mTOR inhibitor.

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Table 1. Epidemiology, Genetic Mutations, and Management of non-clear cell RCC

ncRCC Type	Incidence (Sankin)	Genetic Mutations	Management
Papillary (type 1)	~10-15%	MET alternation (Albiges)	MET inhibitors Consider cabozantinib
Papillary (type 2)		CDKN2A silencing, SETD2 mutations,TFE3fusions, increased NRF2-antioxidant response pathway (Albiges)	Consider sunitinib, pazopanib, cabozantinib
Chromophobe	~5%	TP53, ND5, Folliculin, PTEN (Davis)	Anti VEGF, mTOR inhibitors May benefit from everolimus
Collecting duct	~1%	No specific genetic mutations Genetics overlap to transitional cell carcinomas (Ebel)	Platinum based chemotherapy Consider combination with gemcitabine and bevacizumab
Medullary	<1%	Loss of function of SMARCB1/ INI1 gene (Calderaro)	Platinum based chemotherapy Reports of topoisomerase II chemotherapy Reports of bortezomib (proteasome inhibitor)
Unclassified	5%	No specific genetic mutations	Chemotherapy Consider sunitinib, pazopanib, cabozantinib

represent a distinct subtype but now better understood to represent a nonspecific pattern of high-grade morphology, can be seen in any histologic subtype of RCC. Additionally, there are other types of non-epithelial malignancies that can arise from the kidney including lymphoma, sarcoma, and carcinoid tumors. These tumor types are beyond the scope of the paper and will not be included in the discussion.

The papillary subtype of non-clear cell RCC can be further subdivided into type 1 and type 2 papillary RCC. Type 1 papillary RCC tumors are typically multifocal but slow growing and have low metastatic potential thus patients with type 1 papillary RCC are typically diagnosed at lower stages of disease.[15] These tumors arise from the proximal convoluted tubules of nephrons and demonstrate a predominantly papillary growth pattern with small, basophilic cells of low nuclear grade.[10,12]

Data from The Cancer Genome Atlas (TCGA) has identified alterations in the MET oncogene to be prevalent in most type 1 papillary RCCs.[13-14] Familial types of type 1 papillary RCC are commonly associated with germline MET mutations on chromosome 7 while sporadic type 1 papillary RCCs are more often associated with MET amplification rather than mutation.[11] Both types of papillary RCC are found to have trisomies of chromosomes 7 and 17 and variability in chromosomes 1, 12,16, 20, and Y.[12] Other mutations identified as having a possible association with the papillary subtypes include NF2, SLC5A3, PNKD, CPQ, LRP2, CHD3, SLC9A3R1, SETD2, and CRTC1.[16]

Type 2 papillary RCC is a more aggressive variant with worse outcomes[15] and is histologically distinct with eosinophilic cells with granular cytoplasm and high nuclear grade.[12] This subtype has been noted to have genetic alterations such as CDKN2A silencing, SETD2 mutations, TFE3 fusions, and increased expression of the NRF2-antioxidant response pathway.[13-14] CDKN2A silencing and the CpG island methylation phenotype are associated with a poorer prognosis.[13] Type 2 papillary RCC may exhibit greater VEGF expression and is more often associated with -1p, -3p, and +5q than type 1.[17] This type of RCC can be associated with a germline mutation in the genes involved in the tricarboxylic acid cycle. [18] For example, hereditary leiomyomatosis and RCC syndrome results in a loss-of-function mutation in the fumarate hydratase enzyme. Patients with this syndrome present with skin lesions, uterine leiomyoma, and solitary RCC lesions.[18] Additionally, there have been reports of an association between loss of fumarate hydratase and HIF-1 overexpression and poorer prognosis.[19]

Chromophobe RCC has a solid, tubular, or sarcomatoid growth pattern with cells arising from the intercalated cells of the distal tubules of nephrons.[10,12] The cells are eosinophilic and contain microvesicles that stain for

Table 2. Completed Randomized Trial Evidence in non-clear cell RCC

Trial	ncRCC Types	Sample size (n)	Phase	Treatment	ORR	mOS (months)	mPFS (months)
ESPN	Papillary, chromophobe, translocation, unclassified, sarcomatoid	n=73	II	Sunitinib	9.8%	16.2	6.1
				Everolimus	2.8%	14.9	4.1
ASPEN	Papillary, chromophobe, unclassified	n=51	II	Sunitinib	NR	31.5	8.3
		n=57		Everolimus	NR	13.2	5.6
RECORD-3	NR	n=35	II	Sunitinib	NR	NR	7.2
		n=31		Everolimus	NR	NR	5.1
PANORAMA		n=37	II	Pazopanib	NR	17.2	15.9
SUPAP	Papillary	n=15	II	Sunitinib for type 1 papillary	NR	17.8	6.6
		n=46		Sunitinib for type 2 papillary	NR	12.4	5.5
RAPTOR	Papillary	n=92	II	Everolimus	NR	21	3.9
Foretinib	Papillary	n=74	II	Foretinib	13.5%	NR	9.3
GETUG	Collecting Duct	n=23	II	Gemcitabine with cisplatin or carboplatin	26%	7.1	10.5

ORR: Objective Response Rate, mOS: Median Overall Survival, mPFS: Median Progression Free Survival.

Hale colloidal iron.[12] Commonly seen cytogenetic aberrations include multiple monosomies and loss of chromosomes -1, -2, -6, -10, -13, -17, -21.[20] This type of RCC is typically slow growing, and rarely metastatic, although sarcomatoid histology is associated with a more aggressive phenotype. Common mutations associated include TP53, ND5, and Folliculin[20] and PTEN, FAAH2, PDHB, PDXDC1, and ZNF765 have also been found to be contributory.[17] Birt-Hogg-Dube syndrome is a rare autosomal-dominant disease associated with the Folliculin mutation on chromosome.[17-21] Patients with this disorder present with hamartomas, renal and/or pulmonary cysts, and chromophobe or mixed oncocytoma RCC.[21] Chromophobe RCC has also associated with Cowden syndrome characterized by PTEN mutations.[22]

Collecting Duct RCC or Bellini duct carcinoma is a rare, aggressive tumor that typically metastasizes early and has an overall poor prognosis.[23] The majority of patients with this type are diagnosed with metastatic disease with a median survival of only a few months once metastasized.[23] The cell of origin is the epithelial cell of the collecting ducts. These tumors typically display a tubular or papillary growth pattern. Cells of this tumor type often have positive staining for E-cadherin and c-KIT.[12] The histology and genetics of these cells have features that overlap with transitional cell carcinomas.[10] For example, collecting duct carcinomas can display Her-2 overexpression.[12]

Medullary RCC is another rare subtype similar in morphology to that of collecting duct RCC. It is commonly seen in younger patients who have been diagnosed with sickle cell disease or trait. Medullary RCCs arise from calyceal epithelium and have cystic morphology and inflammation present.[12] Similar to collecting duct RCC, this type is also aggressive, and in fact has a worse median survival than collecting duct RCC.[24] Medullary RCC is associated with a loss of function mutation of the SMARCB1/INI1 gene, which is a chromatin remodelling

Table 3. Targeted Agents for non-clear cell RCC

Type	Agent	Target
VEGF inhibitors	Sunitinib	VEGFR, PDGFR, KIT, RET
	Pazopanib	VEGFR, PDGFR, FGFR, KIT
	Lenvatinib	VEGFR, PDGFR, FGFR, KIT, RET
	Axitinib	VEGFR
	Bevacizumab	VEGF
MET inhibitors	Cabozantinib	MET, AXL, VEGFR, KIT
	Foretinib	MET, AXL, VEGFR
	Capmatinib	MET
	Savolitinib	MET
	Volitinib	MET
	Crizotinib	ALK, MET
mTOR inhibitors	Everolimus	mTOR
	Temserolimus	mTOR
EGFR inhibitors	Erlotinib	EGFR
	Vandetanib	EGFR, VEGFR, RET
Checkpoint inhibitors	Nivolumab	PD-1
	Pembrolizumab	PD-1
	Atezolizumab	PD-L1
	Durvalumab	PD-L1
	Ipilimumab	CTLA-4
Proteosome inhibitor	Bortezomib	Proteosome

regulator and repressor of cyclin D1 transcription.[25] Medullary RCC can also be differentiated from collecting duct RCC by the presence of OCT3/4 protein on immunohistochemistry.[24,26]

Translocation associated RCC are classified on the basis of the chromosome involved (X or 6). The translocation involves fusion of the TFE3 transcription gene with ASPL or PRCC, configuring a distinctive RCC subtype.[27] Most Xp11.2 translocation RCCs occur in pediatric populations however in adults, it presents at an advanced stage and displays an aggressive clinical behavior.[28]

Unclassified RCC represents 5% of non-clear cell RCC. RCC tumors that do not fit other genetic and histopathologic classifications would be categorized as unclassified RCC. Unclassified renal cell carcinoma, which includes tumors that are 100% sarcomatoid in appearance and for which a more definitive tumor histology cannot be assigned, is associated with distinct and highly aggressive biological behavior, and poor clinical outcome. In a single institution study, compared to clear cell carcinoma, patients with unclassified RCC had more metastatic disease at diagnosis, larger tumors, increased risk of adrenal gland involvement, direct invasion to adjacent organs, bone involvement, regional and nonregional lymph node metastases. Unclassified histology was a significant indicator for poor prognosis. Median survival in patients with advanced or metastatic unclassified renal cell carcinoma was 4.3 months.[29]

Current Treatment Landscape for Non-clear Cell RCC

Nephrectomy plays an important and potentially curative role in localized, and an important cytoreductive role in metastatic, non-clear RCC given the suboptimal efficacy of systemic therapy. In metastatic disease, cytoreductive nephrectomy (CN) for non-clear cell RCC showed significantly lower cancer-specific mortality and all-cause mortality among 64% of the patients in the SEER database between 2000 and 2009.[1] Additionally, Vaishampayan and colleagues analyzed advanced non-clear cell RCC cases between 2000 and 2013 from SEER which showed a higher risk of death in patients with non-clear cell RCC when compared to clear cell with a median OS 5 and 7 months respectively.[18] There were 10% more patients with distant-stage non-clear cell RCC who under-

Table 4. Ongoing Clinical Trials for non-clear cell RCC

Trial ID	Phase	Recruiting	Treatment	Line of therapy	Primary endpoint
NCT02724878	II	Non-clear cell RCC	Atezolizumab & bevacizumab	First	ORR
NCT02853344	II	Non-clear cell RCC	Pembrolizumab	First	ORR
NCT02915783	II	Non-clear cell RCC	Lenvatinib & everolimus	First	ORR
NCT03075423	II	Non-clear cell RCC	Nivolumab & ipilimumab vs. sunitinib	First	OS
NCT02982954	IIIb/IV	Non-clear cell RCC	Nivolumab and ipilimumab	First	Incidence of immune-mediated adverse events
NCT01767636	II	Non-clear cell RCC	Pazopanib	Second	OS
NCT01798446	II	Non-clear cell RCC	Axitinib	Second	PFS
NCT02127710	II	Papillary RCC	Savolitinib (AZD6094)	First/Second	ORR
NCT02489695	II	Papillary RCC	Axitinib	Second	24-week PFR
NCT02019693	II	Papillary RCC	Capmatinib (INC280)	Second	ORR
NCT02761057	II	Papillary RCC	Cabozantinib vs. crizotinib vs. savolitinib vs. sunitinib	Second	PFS
NCT02819596	IB/II	Papillary RCC	Durvalumab (MEDI4736) & savolitinib	Second	Dose-limiting toxicity/ORR
NCT02363751	II	Collecting duct RCC	Gemcitabine & platinum & bevacizumab	First	PFS
NCT02504892	II	Chromophobe RCC, BHD-associated renal tumors	Everolimus	Any	ORR
NCT02639182	II	Non-clear subjects must be ENPP3 positive, defined as IHC H-score ––≥15	AGS-16C3F vs. Axitinib	Second	PFS--

ORR: Objective Response Rate, mOS: Median Overall Survival, mPFS: Median Progression Free Survival.

went CN and despite this increase, OS outcomes were worse for non-clear cell RCC.[30]

On the other end of the spectrum, small renal masses with an indolent subtype that are known to be either papillary type 1 or chromophobe could be observed or ablated in selected patients. Currently, outside a clinical trial setting, there is no role for adjuvant systemic therapy as there was no benefit in disease-free survival or overall sur-

vival seen with either sunitinib or sorafenib as compared to placebo from the double-blind randomized ECOG 2805 study that evaluated a subgroup of non-clear cell patients (550 of 1943) with localized RCC post nephrectomy.[30] In high-risk patients with medullary, or collecting duct carcinoma, adjuvant platinum-based chemotherapy should be considered.[31]

For patients with advanced recurrent or metastatic disease, the treatment of choice is systemic therapy. Although there have been significant advances in the treatment of metastatic RCC in the post-cytokine era, the majority of studies to date have mostly involved clear-cell RCC with a subset of patients with non-clear cell histology. It is noteworthy to mention that the efficacy of the same agents in non-clear cell RCC is reduced with decreased response rates and shorter durations of response.[30] Given the fatal disease and the lack of randomized clinical trials as well as no specific FDA approvals, the general approach to management of non-clear cell metastatic RCC is similar to that of clear cell; however subtype specific clinical trials are evolving (**Table 4**).

Papillary

The phase II ASPEN trial is one of the largest trials that support the use of VEGF inhibitors in papillary cancer (**Table 2**). In this study 108 previously untreated non-clear cell RCC patients (68 with papillary, 16 with chromophobe, and 22 with unclassified) were randomized to either sunitinib or everolimus. Median PFS, which was the primary endpoint, was longer in patients assigned to the sunitinib arm. Compared with everolimus, sunitinib showed a longer PFS (8.3 vs 5.6 months), and higher objective response (18% versus 9%). Interestingly, subgroup analysis for the good and intermediate-risk group had longer PFS (14 months versus 5.7 months for good risk and 6.5 versus 4.9 months for intermediate-risk), compared to the poor-risk group that had shorter PFS with sunitinib compared with everolimus (4.0 versus 6.1 months).[32]

The ESPN trial is a phase two study that randomly assigned treatment with everolimus or sunitinib to 73 patients with metastatic non-clear cell RCC (27 papillary, 12 chromophobe, 7 translocation, 10 unclassified, and 12 sarcomatoid) with crossover to the other arm at disease progression. The study concluded that everolimus was not superior to sunitinib as both PFS and overall survival did not show any statistical difference between the two groups (16.2 versus 14.9 months) for the initial treatment with sunitinib and everolimus respectively.[33]

RECORD-3 trial is a phase two study that compared the sequence of sunitinib followed by everolimus versus everolimus followed by sunitinib in first-line metastatic RCC (including both clear cell and non-clear cell type. A total of 66 non-clear cell RCC patients were included in the analysis and there was a trend toward a longer PFS with sunitinib as the initial treatment as compared with everolimus (7.2 versus 5.1 months).[34]

A phase II PANORAMA trial of pazopanib in non-clear cell RCC reported an 81% disease control rate and partial responses in 27% of patients (10 of 37). Median PFS was 15.9 and OS were 17.2 months.[35]

In 2015, the SUPAP phase two study enrolled 61 patients with metastatic papillary RCC (15 with type 1 and 46 with type 2) who were treated with sunitinib with results showing overall survival of 17.8 and 12.4 months and PFS of 6.6 and 5.5 months, in type 1 and 2 papillary RCC, respectively.[36] Subsequently, the phase 2 RAPTOR trial in 2016 enrolled 92 patients with papillary RCC treated with everolimus demonstrating an overall survival of 21 months, and PFS of 3.9 months.[37]

A phase II trial that was presented in 2014 European Organisation for Research and Treatment of Cancer-National Cancer Institute-American Association for Cancer Research (EORTC-NCI-AACR) included 41 patients with papillary RCC who were treated with bevacizumab in combination with erlotinib (an epidermal growth factor receptor). This combination demonstrated a 30% objective response rate both groups that had sporadic disease and hereditary leiomyomatosis and renal cell cancer. The median PFS was 24 months for those with hereditary leiomyomatosis compared to only seven months with sporadic papillary RCC.[38]

As discussed previously met oncogene plays a significant role in papillary cancer. With that knowledge, several clinical trials with MET directed-therapies have shown activity in papillary RCC.

In a recent EORTC 90101 CREATE phase II trial, the ALK-inhibitor crizotinib, which appears to have affinity for MET kinase, has shown activity among MET-positive papillary RCC type 1. Schöffski and colleagues treated 23 eligible patients out of 41. The response rate was 50% for patients that were MET-positive (2 out of 4 patients) with a mean treatment duration noted to be longer in the MET altered cohort (11.9 versus 5.3 months).[39]

Additionally, a randomized phase II SWOG 1500 PAPMET clinical trial will evaluate a total of 180 patients with metastatic type 1 and type 2 papillary RCC to receive either sunitinib, crizotinib, cabozantinib (a dual VEGFR2/MET inhibitor), or savolitinib (a distinct and more specific MET inhibitor). This study is currently ongoing and recruiting patients.[40]

Foretinib is a multi-targeted TKI that targets MET and VEGF receptors that has demonstrated some benefit in papillary RCC based on a phase II trial that included 74 patients. The ORR was 13.5% and the median PFS was 9.3 months. However, the RR was 50% in patients with germline MET mutation. The OS was 70% at one year.[41]

In a similar phase II trial that evaluated another MET inhibitor, Savolitinib, for 109 patients with papillary RCC, there was an ORR of 7% and tumor shrinkage in 20%. For the 40% of patients with MET-driven disease, the ORR was noted to be 18% (8 out of 44 patients) and tumor shrinkage in 61%. The median PFS was 6.2 months compared to 1.4 months with MET-negative papillary RCC which was statistically significant with a hazard ratio of 0.33 in favor of MET-driven papillary RCC as compared to

the non-MET driven disease. Additionally, there were no partial responses seen in the 46 tumors that were not driven by MET.[42] Currently, there is an ongoing phase III SAVOIR trial, comparing savolitinib with sunitinib to determine whether or not savolitinib has selective activity in a MET-selected population (NCT03091192).[43] There is another randomized trial evaluating the clinical efficacy of three distinct targeted therapies including volitinib (MET inhibitor), cabozantinib (VEGF, MET, AXL inhibitor), and crizotinib (ALK-1 and MET inhibitor) with sunitinib as the comparator control arm (NCT02761057).[44] If either of these studies is positive, it would herald a change in the current standard of care for frontline treatment in metastatic papillary RCC.

As the landscape of treatment for clear cell RCC has shifted to immunotherapy due to the CheckMate 214 that suggested an OS advantage with the combination of nivolumab/ipilimumab over sunitinib in the first-line setting, there is biological rationale to extrapolate the activity of immunotherapy in non-clear cell RCC. Choueiri et al. have evaluated 101 patients with a variety of non-clear cell subtypes and found varied expression levels of PD-L1 in this cohort, with 10% of papillary patients expressing PD-L1 in tumor cells.[45] Additionally, A retrospective analysis with a PD-1 inhibitor, nivolumab monotherapy, was done for 41 patients with non-clear cell histology that included 16 papillary, 14 unclassified, 5 chromophobe, 4 collecting duct, and 1 Xp11 translocation. There were 20% of patients that had a PR and 29% with stable disease. Responses were observed in unclassified, papillary, and collecting duct subtypes which lend support to the use of nivolumab for patients with non-clear cell RCC.[59] Currently there are studies of dual immuno- therapy that include a non-clear cell arm that will provide additional insight into the activity of checkpoint inhibitors in this population. There are ongoing phase II studies with a PD-L1 inhibitor, atezolizumab, in combination with a VEGF inhibitor, bevacizumab, in patients with advanced non-clear cell RCC (NCT02724878), thought no results have yet been reported.[46]

Overall, for papillary RCC, VEGR-targeted therapies seem to be the most effective first-line treatment for both type 1 and type 2 papillary RCC. mTOR inhibitor, however, has been shown to have activity in treating papillary type RCC and can be used as a second-line therapy option.

Chromophobe

Both VEGF receptor inhibitors and mammalian target of rapamycin (mTOR) inhibitors have been used to treat chromophobe RCC. In the ASPEN trial, subgroup analysis of chromophobe RCC demonstrated better clinical outcomes with everolimus therapy.[32] In 2008, a study looked at 53 patients with non-clear cell RCC (41 with papillary and 12 with chromophobe) treated with sunitinib or sorafenib. The results for the 12 chromophobe type RCC (7 treated with sunitinib and 5 with sorafenib) showed a response rate of 25% to sunitinib or sorafenib, PFS of 10.6 months (sorafenib treated group had a longer median PFS of 27.5 months).[47] In the ESPN trial, which included 12 chromophobe RCC subtype, there was an objective response rate of 2.8% and 6%, and overall survival was 25.1 and 31.6 months for the everolimus and sunitinib treated groups, respectively.[33]

Collecting Duct

Collecting duct RCC, due to its similarities with transitional cell carcinoma, is treated with chemotherapy with a platinum based regimen as well as with combination chemotherapy and bevacizumab. In 2007, a phase two prospective multicenter study evaluated 23 patients with metastatic collecting duct carcinoma treated with gemcitabine plus either cisplatin or carboplatin. Results of the study demonstrated an objective response of 26%, with a PFS of 7.1 months and an overall survival 10.5 months.[48] Another study in 2013, enrolled 5 patients with metastatic collecting duct RCC who were treated with gemcitabine plus a platinum-based agent in addition to bevacizumab. Three of the cases had partial response, one with stable disease, and another one with a complete remission. Median overall survival was 27.8 months and PFS was 15.1 months.[49]

> "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."

Medullary

Medullary RCC is typically treated with a platinum-based chemotherapy regimen, but because it is such a rare disease, data is still lacking to clearly support a first line regimen. There are multiple case reports of medullary RCC responding to combination chemotherapy with gemcitabine, paclitaxel and a platinum agent.[50-51] Treatment with a topoisomerase II chemotherapy, such as etoposide has shown efficacy based on a patient who achieved complete response for 9 months after receiving a topoisomerase II therapy.[52] Another case report looked at two patients with renal medullary carcinoma receiving combination platinum-based therapy with bortezomib, a proteasome inhibitor, with promising results: one patient passing away 7 years after diagnosis, while another remains disease free nearly 2 years from diagnosis.[53] In 2004 a phase two study recruited 37 patients with metastatic renal cell RCC (25 clear cell, 6 papillary, 1 collecting duct, 1 medullary, and 4 unspecified) who were treated with bortezomib.[54] On a follow up report to this study, the patient with medullary RCC received 7 months of bortezomib, achieved a complete response, and remain without evidence of disease after 27 months.[55]

Unclassified/Translocation

There are scant data available for unclassified and translocation RCC. Although no prospective trials have been conducted in this setting, there are case reports that document the activity of VEGF-targeted agents. For patients with Xp11.2 translocation, one study reported 15 patients with had received VEGF-directed therapies. Three patients (20%) achieved a partial response. The median PFS was 7.1 months and medians OS was 14.1 months.[56] The Juvenile RCC network reported a series of 11 patients who received sunitinib in the first-line setting with a median PFS of 8.2 months.[57]

Conclusion

With no clear standard of care FDA approved agents, non-clear cell RCC represents a significant and long ongoing unmet medical need. Patients should be encouraged to participate in clinical trials whenever possible, though given the heterogeneity of this disease, investigators should not make the mistake of combining numerous non-clear cell RCCs in prospective trial designs. Instead, each non-clear cell histology has its unique characteristics and should be studied individually. 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; however, there are ongoing studies that show promising results, notably in papillary RCC with sarcomatoid and rhabdoid features. Combinations with a PD-1 inhibition with CTLA-4 inhibitors, or ido-1 inhibitors are noteworthy and currently in study. As we gain a better understanding of the biology through the discovery of molecular and genomic testing, collaborative efforts will be essential for the therapeutic development of targeted pathways and agents to further advance this orphan disease.

> "As the landscape of treatment for clear cell RCC has shifted to immunotherapy due to the CheckMate 214 trial that suggested an OS advantage with the combination of nivolumab/ipilimumab over sunitinib in the first-line setting, there is biological rationale to extrapolate the activity of immunotherapy in non-clear cell RCC."

References

1. National Cancer Institute's Surveillance, Epidemiology, and End Result (SEER) Program data
2. Welch HG, Skinner JS, Schroeck FR, et al. Regional Variation of Computed Tomographic Imaging in the United States and the Risk of Nephrectomy. *JAMA Intern Med.* 2018Feb 1;178(2):221-227.
3. Zeegers MPA, Tan FES, Dorant E, van den Brandt PA. The impact of characteristics of cigarette smoking on urinary tract cancer risk : a meta-analysis of epidemiologic studies. *Cancer*. 2000;89:630–639.
4. Inoue M, Iwasaki M, Otani T, Sasazuki S, Noda M, Tsugane S. Diabetes mellitus and the risk of cancer: results from a large-scale population-based cohort study in Japan. *Arch Intern Med*. 2009;166:1871–1877.
5. Setiawan VW, Kolonel LN, Henderson BE. Menstrual and reproductive factors and risk of renal cell cancer in the Multiethnic Cohort. *Cancer Epidemiol Biomerkers Prev.* 2009;18:337–340.
6. Chiu WA, Caldwell JC, Keshava N, Scott CS. Key scientific issues in the health risk assessment of trichloroethylene. *Environ Health Perspect*. 2006;114:1445–1449.
7. Chow WH, Dong LM, Devesa SS et al. Nat Rev Urol. 2010; May 7(5): 245-257.
8. Cook MB, et al. Sex disparities in cancer incidence by period and age. *Cancer Epidemiol Biomarkers Prev*. 2009;18:1174–1182.
9. Curado MP, et al., editors. IARC Scientific Publications No. 160. Lyon: IARC; 2007. Cancer Incidence in Five Continents, Vol. IX.
10. Eble JN, Sauter G, Epstein JI, et al. *Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs*. Lyon, France; IARC Press; 2004.
11. Sankin A, Hakimi AA, Hsieh JJ, et al. Metastatic Non-Clear Cell Renal Cell Carcinoma: An Evidence Based Review of Current Treatment Strategies. *Frontiers in Oncology*. 2015; 5:67.
12. Liaw BC, Mehrazin R, Baker C, et al. Management of Atypical Renal Cell Carcinomas. *Curr.Treat.Options in Oncol.* (2017) 18:61.
13. The Cancer Genome Atlas Research Network Comprehensive molecular characterization of papillary renal-cell carcinoma. *New England Journal of Medicine*. 2016; 374: 135-145.
14. Albiges I, Guegan J, Le Formal A, et al. MET is a potential target across papillary renal cell carcinomas: result from a large molecular study of pRCC with CGH array and matching gene expression array. *Clin Cancer Res*. 2014;20(13):3411-21.
15. Srigley JR, Delahunt B, Ebel JN, et al. ISUP Renal Tumor Panel. The International Society of Urological Pathology (ISUP) Vancouver Classification of Renal Neoplasia. *American Journal of Surgical Pathology*. 2013; 37(10):1469-1489.
16. Durinck S, Stawiski EW, JimenezAP et al. Spectrum of diverse genomic alterations define non-clear cell renal carcinoma subtypes. Nature genetics. 13-27(2015).
17. Klatte T, Pantuck AJ, Said JW et al. Cytogenetic and molecular tumor profiling for type 1 and type 2 papillary renal cell carcinoma. *Clin Cancer Res*. 2009; 15:1162.
18. Wei MH, Toure O, Glenn GM, et al. Novel mutations in FH and expansion of the spectrum of phenotypes expressed in families with hereditary leiomyomatosis and renal cell cancer. *Journal of Medical Genetics*. 2006; 43: 18-27.
19. Isaacs JS, Jung YJ, Mole DR et al. HIF overexpression correlates with biallelic loss of fumarate hydratase in renal cancer: novel role of fumarate in regulation of HIF stability. *Cancer Cell*. 2005;8(2): 143-53.
20. Davis CF, Ricketts CJ, Wang M, et al. The somatic genomic landscape of chromophobe renal cell carcinoma. *Cancer Cell*. 2014; 26(3): 319-330.
21. Nickerson ML, Warren MB, Toro JR, et al. Mutations in a novel gene lead to kidney tumor, lung wall defects, and benign tumors of the hair follicle in patients with the Birt-Hogg-Dube syndrome. *Cancer Cell*. 2002; 2: 157-164.
22. Habib SL, Al-Obaidi NY, Nowacki M, et al. Is mTOR inhibitor good enough for treatment all tumor in TSC patients? *J Cancer*. 2016;7(12): 1621-31.
23. Motzer RJ, Bacik J, Mariani T, et al. Treatment outcome and survival associated with metastatic renal cell carcinoma of non-clear cell histology. *Journal of Clinical Oncolology*. 2002; 20:2376-2381.
24. Gupta R, Billis A, Shah RB, et al. Carcinoma of the collecting ducts of Bellini and renal medullary carcinoma: clinicopathologic analysis of 52 cases of rare aggressive subtypes of renal cell carcinoma with a focus on their interrelationship. *The American Journal of Surgical Pathology*. 2012; 36(9):1265-78.
25. Calderaro J, Moroch J, Pierron G, et al. SMARCB1/INI1 inactivation in renal medullary carcinoma. *Histopathology*. 2012; 61(3):428-435.
26. Rao P, Tannir NM, Tamboli P, et al. Expression of OCT3/4 in renal medullary carcinoma represents a potential diagnostic pitfall. *Am J Surg Pathol*. 2012; 36(4):583-588.
27. Medendorp K, van Groningen JJ, Vreede L, et al. The renal cell carcinoma-associated oncogenic fusion protein PRCCTFE3 provokes p21 WF1/CIP1-mediated cell cycle delay. *Exp Cell Res*. 2009;315:23992409.
28. Mir MC, Trilla E, de Torres IM, et al. Altered transcription factor E3 expression in unclassified adult renal cell carcinoma indicates adverse pathological features and poor outcome. *BJU Int*. 2011: 108:e71-6.
29. Zisman A, Chao DH, Pantuck AJ, et al. Unclassified renal cell carcinoma: clinical features and prognostic impact of a new histological subtype. *The Journal of Urology*. 2002; 168(3):950-5.
30. Haas NB, Manola J, Uzzo RG, et al. Adjuvant sunitinib or sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOG-ACRIN

E2805): a double-blind, placebo-controlled, randomised, phase 3 trial. Lancet. 2016; 387(10032): 2008-16.
31. Staehler M, Haseke N, Schoppler G, et al. Carcinoma of the collecting ducts of Bellini of the kidney: adjuvant chemotherapy followed by multikinase-inhibition with sunitinib. *Eur J Med Res*. 2008;13:531–5
32. Armstrong AJ, Halabi S, Eisen T, et al. Everolimus versus sunitinib for patients with metastatic non-clear cell renal cell carcinoma (ASPEN): a multicentre, open-label, randomised phase 2 trial. *The Lancet Oncology*. 2016; 17(3): 378-388.
33. Tanir NM, Jonasch E, Albiges L, et al. Everolimus Versus Sunitinib Prospective Evaluation in Metastatic Non–Clear Cell Renal Cell Carcinoma (ESPN): A Randomized Multicenter Phase 2 Trial. *European Urology*. 2016; 69(5): 866-874.
34. Motzer RJ, Barrios CH, Kim TM, et al. Phase II Randomized Trial Comparing Sequential First-Line Everolimus and Second-Line Sunitinib Versus First-Line Sunitinib and Second-Line Everolimus in Patients With Metastatic Renal Cell Carcinoma. *Journal of Clinical Oncology*. 2013; 32(25): 2765-2772.
35. Buti S, Bersanelli M, Maines F, et al. First-line Pazopanib in Non-clear cell renal cell carcinoma: the Italian Retrospective Multicenter PANORAMA Study. *Clin Genitourin Cancer*. 2017; 15(4):e609-e614.
36. Ravaud A, Oudard S, De Fromont M, et al. First-line treatment with sunitinib for type 1 and type 2 locally advanced or metastatic papillary renal cell carcinoma: a phase II study (SUPAP) by the French Genitourinary Group. *Annals of Oncology*. 2015; 26(6): 1123-1128.
37. Escudier B. Molinie V, Bracarda S, et al. Open-label phase 2 trial of first-line everolimus monotherapy in patients with papillary metastatic renal cell carcinoma: RAPTOR final analysis. *European Journal of Cancer*. 2016; 69:226-235.
38. Srinivasan R, et al: Mechanism based targeted therapy for hereditary leiomyomatosis and renal cell cancer (HLRCC) and sporadic papillary renal cell carcinoma: interim results from a phase 2 study of bevacizumab and erlotinib. EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics. Abstract 5. Presented November 19, 2014.
39. Schoffski P. Crizotinib achieves objective responses and long-lasting disease control in patients with metastatic papillary renal cell carcinoma type 1 (PRCCC1) with somatic MET mutations. EORTC phase II trial 90101 "CREATE". Paper presented at: American Association of Cancer Research Annual Meeting 2016; April 2016; New Orleans, LA.
40. Https://clinicaltrials.gov NCT02761057
41. Choueiri TK, Vaishampyan U, Rosenberg JE, et al. Phase 2 and biomarker study of the dual MET/VEGFR2 inhibitor foretinib in patients with papillary renal cell carcinoma. *J Clin. Oncol*. 2013; 31(2):181-6.
42. Choueiri TK, Plimack E. Arkenau HT et al. Biomarker-based phase II trial of savolitinib in patients with advanced papillary renal cell cancer. *J Clin Oncol*. 2017; 35(26):2993-3001.
43. https://clinicaltrials.gov: NCT03091192
44. https://clinicaltrials.gov NCT02761057
45. Choueiri TK, Fay AP, Gray KP, et al. PD-L1 expression in nonclear-cell renal cell carcinoma. Ann Oncol 2014; 25:2178.
46. https://clinicaltrials.gov NCT02724878
47. Choueiri TK, Plantade A, Elson P, et al. Efficacy of sunitinib and sorafenib in metastatic papillary and chromophobe renal cell carcinoma. *Journal of Clinical Oncology*. 2008; 26(1): 127-131.
48. Oudard S, Banu E, Viellefond A, et al. Prospective multicenter phase ii study of gemcitabine plus platinum salt for metastatic collecting duct carcinoma: results of a getug (Groupe d'Etudes des Tumeurs Uro-Genitales) study. *Journal of Urololgy*. 2007; 177: 1698–702.
49. Pecuchet N, Bigot F, Gachet J, et al. Triple combination of bevacizumab, gemcitabine and platinum salt in metastatic collecting duct carcinoma. *Annals of Oncology*. 2013; 24(12): 2963-2967.
50. Strouse JJ, Spevak M, Mack AK, et al. Significant responses to platinum-based chemotherapy in renal medullary carcinoma. *Pediatric Blood Cancer*. 2005. 44(4): 407-411.
51. Walsh A, Kelly DR, Vaid YN, et al. Complete response to carboplatin, gemcitabine, and paclitaxel in a patient with advanced metastatic renal medullary carcinoma. *Pediatric Blood Cancer*. 2010; 55(6): 1217-1220.
52. Schaeffer EM, Guzzo TJ, Furge KA et al. Renal medullary carcinoma: molecular, pathological and clinical evidence for treatment with topoisomerase-inhibiting therapy. *BJU Int*. 2010 Jul;106(1):62-5.
53. Carden MA, Smith S, Meany H, et al. Platinum plus bortezomib for the treatment of pediatric renal medullary carcinoma: Two cases. Pediatric Blood Cancer. 2017. 64(7).
54. Kondagunta GV, Drucker B, Schwartz L, et al. Phase II Trial of Bortezomib for Patients With Advanced Renal Cell Carcinoma. *Journal of Clinical Oncology*. 2004; 22(18): 3720-3725.
55. Ronnen EA, Kondagunta GV, Motzer RJ, et al. Medullary Renal Cell Carcinoma and Response to Therapy with Bortezomib. *Journal of Clinical Oncology*. 2006; 24(9): e14-e14.
56. Choueiri TK, Lim ZD, Hirsch MS, et al. Vascular endothelial growth factor-targeted therapy for the treatment of adult metastatic Xp11.2 translocation renal cell carcinoma. *Cancer*. 2010;116:5219.
57. Malouf GG, Camparo P, Oudard S, et al. Targeted agents in metastatic Xp11 translocation/TFE3 gene fusion renal cell carcinoma (RCC): a report from the Juvenile RCC Network. *Ann Oncol*. 2010;21:1834-1838.
58. Geynisman, DM. Anti-programmed Cell Death Protein 1 (PD-1) Antibody Nivolumab Leads to a Dramatic and Rapid Response in Papillary Renal Cell Carcinoma with Sarcomatoid and Rhabdoid Features. *Eur Urol*. 2015; 68:912.
59. Koshkin VS, Barata PC, Zhang T, et al. Clinical activity of nivolumab in patients with non-clear cell renal cell carcinoma. *Journal for ImmunoTherapy of Cancer*. (2018)6:9. KCJ

Late Relapsing Renal Cell Carcinoma: A Brief Review Suggests Expected PFS and OS 5 Years and Beyond after Nephrectomy

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Introduction

In the past decade, the treatment of renal cell carcinoma (RCC) has advanced more rapidly than at any other time in medical history. Better imaging techniques have led to increased detection of small, localized lesions, leading to higher rates of resection with curative intent.[1] Partial nephrectomies and other nephron-sparing approaches have also been refined. And, of course, major advancements in systemic therapies including the development of oral targeted therapies and immune checkpoint inhibitors have led to unprecedented improvements in outcomes for patients with advanced, unresectable disease. However, despite these advances, of those patients who undergo resection of RCC with curative intent, approximately 30% still recur with most of those developing distant metastatic disease.[2] Adjuvant therapy to prevent such recurrence is still largely under investigation with many negative trials to date. Only sunitinib has recently been approved for adjuvant use, and is generally recommended for selected patients at higher risk of recurrence.

Most post-surgical relapses of RCC occur within 2 years of resection. Rapid recurrence, especially within one year of definitive surgery, is associated with poorer prognosis and more aggressive disease. The widely used Motzer/MSKCC risk stratification model[3] uses recurrence within a year as one of its elements used to categorize risk, as does the Heng criteria[4] and other risk stratification models. So, if early recurrence is associated with poorer outcomes, is later recurrence associated with better outcomes?

Late Relapse - Beyond Five Years

Adamy and colleagues analyzed characteristics in patients with recurrent RCC 5 years or later after nephrectomy to determine predictors of survival after recurrence. They analyzed a total of 2,368 nephrectomy cases and found that 256 patients had disease recurrence, and 44 of those had their disease relapse 5 years or more after nephrectomy. They found that patients with late recurrence originally had fewer symptoms at initial presentation, smaller primary tumors (median 8.5 vs 7 cm) and less aggressive disease (pT1 in 18% vs 39%). Median overall survival from the time of recurrence was 6.1 years. A multi-variant analysis found that longer survival was associated with a favorable Motzer/MSKCC risk score and the absence of symptoms related to metastasis.[5]

Our group conducted a retrospective study to access outcomes in patients with recurrence >5 years after definitive nephrectomy. We retrospectively reviewed clinical data on consecutive patients treated with targeted therapy for mRCC who were diagnosed >5 years after nephrectomy with curative intent between November 1, 2006, and November 1, 2013. Patients with a history of either radical or partial nephrectomy were included. Patients were excluded if they had evidence of metastases at the time of surgery or at any time prior to five years beyond surgery. Of the 520 patients with stage I-III RCC who underwent definitive complete or partial nephrectomies, 28 were found to have relapsed beyond 5 years, with a median time between nephrectomy and recurrence of 8.3 years. Most were categorized as favorable risk (71%) with only 1 patient having poor risk features, and all had clear cell histology. Most (83%) presented with multiple sites of metastases, with lung being the most common (79%) and bone and pancreases as second most common (both 33%). We also noted a high number of unusual sites of metastases including bowel, pleura, muscle, and abdominal wall, a phenomenon that has been reported in other studies of late relapsing RCC and in several case reports.[6,7,8]

The estimated median overall survival time in our patients was 60.5 months after detection of metastatic disease, and the 3-year overall survival rate after detection of metastatic disease was 71.78% (95% CI, 47.98%-84.77%). This is similar to that reported in Adamy's finding and other analyses. All of our patients were treated with targeted therapy, with median time to treatment failure on first-line therapy of 19.7 months (range, 0.5- 41.6). We

Keywords: Late relapsing renal cell carcinoma, recurrence of kidney cancer more than 5 years following nephrectomy, targeted therapy.

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found no significant difference in time to treatment failure between therapies, although our analysis was certainly not powered or designed to do so.

Park, et al undertook an analysis of 747 patients who had undergone curative surgery for RCC, with 41 patients found to have developed recurrent RCC >5 years. The researchers focused their analysis on clinic-pathological features found in late relapsing patients and indentifying risk factors associated with late relapse. They found that late relapsing patients had a higher hemoglobin level and lower ESR, in addition to favorable pathological features, such as lower pT stage, favorable Fuhrman's nuclear grade, and absence of: tumor necrosis, sarcomatoid differentiation, and lymphovascular invasion. They identified several clinical and pathological factors that were strongly associated with high-er risk of late recurrence in patients with RCC—the most important were more advanced age and higher serum hs-CRP levels at diagnosis.

The five-year cancer-specific survival rate in this series of late relapsing patients was 73.7%, compared to 41.1% in earlier relapsing patients (*P*=<0.001). As in previous studies Park and colleagues also showed that a significant number of patients with late recurrence developed metastatic disease at unusual sites, such as the pancreas, thyroid, scalp, and submandibular gland.[9]

Santoni and colleagues pooled data 21 Italian centers and that out of 2,490 patients who had relapsed RCC after nephrectomy, 269 (11%) occurred >5 years after surgery.[10] Their study focused on outcomes with first line therapies, of which 190 patients (71%) were treated with sunitinib, 58 (21%) with sorafenib and 21 (8%) with pazopanib. Median progression-free survival was 20.0 months for sunitinib (95% CI 17.0-25.1), and 14.1 months for both sorafenib (95% CI 11.0-29.0) and pazopanib (95% CI 11.2-NA). They found that MSKCC score and lymph nodes, liver, and brain metastases were associated with worst overall survival, while pancreatic metastases were associated with longer survival, an observation Kalra and others have also made.[11]

Santoni et al undertook another analysis aimed at assessing the prognostic role of pretreatment immune status as measured by neutrophilia, lymphocytopenia, and neutrophil to lymphocyte ratio (NLR) in patients treated with vascular endothelial growth factor-tyrosine kinase inhibitors (VEGFR-TKIs) for late relapsing (>5 years) RCC. Data was pooled from 13 medical centers in Italy. They identified 151 patients, 56 (37 %) had NLR ≥3 at the start of VEGFR-TKI therapy, while 95 had NLR <3 (63 %). They found a significant difference in median overall survival (OS) in the two groups with those with the higher NLR having a medical OS of 28.8 months and those with a lower NLR achieving an median OS of 68.7 months (p< 0.001). The median progression-free survival (PFS) was 15.8 months higher NLR group and 25.1 months in lower NLR group, also a significant difference (p=0.03). A multivariate analysis revealed that MSKCC risk group and NLR were independent prognostic factors for both OS and PFS in patients with late relapsing RCC.[12]

While most studies suggest that higher stage is a risk factor for relapse, late relapse can occur in early stage RCC following nephrectomy. Ha and colleagues undertook a large retrospective study of 3,567 patients who underwent partial or complete nephrectomy for T1 clear cell RCC between 1999 and 2011 at 5 institutions in Korea. 423 patients remained free of disease for at least 5 years and had adequate follow-up for analysis. During a median follow-up period of 83.9 months (range 60.0- 156.4 months) recurrence was observed in 14 of the 423 (3.3%) patients studied. Symptoms at diagnosis and pathologic T stage were independent predictive factors for late recurrence and patients who presented with symptoms at the time of original diagnosis or who originally had stage T1b disease had a significantly shorter time to late recurrence as compared to those who were asymptomatic or had stage T1a disease at original diagnosis.[13]

"As next generation sequencing becomes more widespread and informatics continues to improve, it will be fascinating to see if patterns emerge that might be able to select those at higher risk for late recurrence based on mutational analysis or whole tumor genomic sequencing."

Very Late Relapse - Beyond Ten Years

Single cases in the published literature report relapses of RCC occurring 25 years or more following nephrectomy,[14] but little is known about outcomes in patients with very late relapsed RCC (greater than 10 years after initial surgery). It is generally thought that these patients tend to have more indolent disease, and small retrospective series tend to suggest this as well.

We undertook a retrospective study on consecutive patients with RCC who had disease recurrence >10 years after nephrectomy for curative intent and were treated with targeted therapies between 11/1/2006 and 11/1/2013 at our center. Among 720 RCC patients treated with nephrectomy, we identified 8 who developed recurrent metastatic disease after a >10 year disease free interval (median: 16.7 years; range: 11.7-29.0). We were careful to exclude patients who may have developed a second primary RCC years after their first diagnosis. Although the number is very small, the results were intriguing. All 8 patients presented with clear cell histology and 88% had favorable disease by IMDC and MSKCC risk stratification models.

All patients presented with multiple metastatic lesions, with the most common sites being lung and bone, although unusual sites, such as soft tissue, pancreas and adrenal were also detected. These patients responded well to targeted therapies (pazopanib and sunitinib) with the median time on first-line treatment of 20.1 months. The median number of sequential targeted therapies received was 2 (with a range of 1-4). Four patients died prior to the analysis. Median OS was found to be 46.6 months (range:

9.8-129), 3 year OS rate was 63%. The most common adverse events to targeted therapies in these patients were fatigue (88%), anorexia (38%) and diarrhea (50%), with 94% of all AEs reported being grade 1 or 2.[15]

Based on the above data, although rare, it is clear that patients are at life-long risk of recurrence after resection of localized RCC as it is possible for metastases to present >10 years after resection. Patients in our study had relatively large metastatic burden and a wide distribution of metastatic sites, insights that may be useful clinically during surveillance. Our cohort demonstrated favorable prognostic features and outcomes when compared to historical controls.

Carrobio and colleagues examined the records of 554 RCC patients who had a negative follow-up during their first 10 years following radical or partial nephrectomy. They found patients 29 (5.2%) patients who experienced disease progression after 10 years, with median occurrence in this group occurring at 13.4 years following surgery. Relapse occurred most commonly in the contralateral kidney (suggesting possible second primary in some of these cases), lung, bone, and liver. Relapse was also seen atypical sites, such as the pancreas and thyroid.[16]

Abara et al reported three cases of RCC relapsing more than 10 years following nephrectomy. All of the patients had relatively indolent recurrent disease, with two of them having developed oligometastatic disease and where rendered no evidence of disease after metastectomy. The third had stable disease for over four years on sorafenib.[17]

Conclusions

Late recurrence of RCC following definitive surgical resection is a known biologic behavior of RCC. Studies have characterized patients with late relapse, occurring after a disease-free interval >5 years or more, in terms of patient and tumor prognostic features and outcomes. Patients with late relapse seem to have lower T stage initial diagnosis, lower Furhman grade tumors, and generally less aggressive disease. It is certainly not surprising, as patients with more higher grade features and more aggressive disease likely recur earlier, leaving most only those patients with more indolent disease vulnerable to late recurrences.

Outcomes in patients with late relapse generally appear to be better than those relapsing earlier with longer survival times and longer response to systemic therapies, although much more research is needed to draw definitive conclusions.

The data which do exists suggest that an individualized approach to adjusting surveillance protocols may be necessary, perhaps by increasing the length of surveillance in patients with a higher propensity to relapse after 5 years.

As research in this area evolves, a next rational step would be to look beyond clinical and pathologic makers that might be associated with late relapsing RCC and explore associations with genetic and molecular markers. As next generation sequencing becomes more widespread and informatics continues to improve, it will be fascinating to see if patterns emerge that might be able to select those at higher risk for late recurrence based on mutational analysis or whole tumor genomic sequencing. Doing so may allow for more accurate selection of patients for longer term screening following definitive surgery, bringing us one step closer to true precision oncology in this subset of patients.

References

1. Znaor A, Lortet-Tieulent J, Laversanne M, Jemal A, Bray F. International variations and trends in renal cell carcinoma incidence and mortality. *Eur Urol.* 2015 Mar;67(3):519-530.
2. Sun M, Thuret R, Abdollah F, et al. Age-adjusted incidence, mortality, and survival rates of stage-specific renal cell carcinoma in North America: a trend analysis. *Eur Urol.* 2011 Jan;59(1):135-141.
3. Motzer RJ, Mazumdar M, Bacik J, Berg W, Amsterdam A, Ferrara J. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. *J Clin Oncol.* 1999 Aug;17(8):2530-40.
4. Heng DY, Xie W, Regan MM, Warren MA, Golshayan AR, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. *J Clin Oncol.* 2009 Dec 1;27(34):5794-9.
5. Adamy A, Chong KT, Chade D, Costaras J, Russo G, et al. Clinical characteristics and outcomes of patients with recurrence 5 years after nephrectomy for localized renal cell carcinoma. *J Urol.* 2011 Feb;185 (2):433-8.
6. Santoni M, Conti A, Porta C, et al. Sunitinib, pazopanib or sorafenib for the treatment of patients with late relapsing metastatic renal cell carcinoma. *J Urol.* 2015 Jan;193(1):41-47.
7. Kroeger N, Choueiri TK, Lee JL, et al. Survival outcome and treatment response of patients with late relapse from renal cell carcinoma in the era of targeted therapy. *Eur Urol.* 2014 Jun; 65(6):1086-1092.
8. Horger DC, Bissada NK, Curry NS, Chaudhary UB. Isolated late recurrence of renal cell carcinoma in the inferior vena cava. *Can J Urol.* 2004 Dec;11(6):2467-9.
9. Park YH, Baik KD, Lee YJ, Ku JH, Kim HH, Kwak C. Late recurrence of renal cell carcinoma >5 years after surgery: clinicopathological characteristics and prognosis. *BJU Int.* 2012 Dec;110(11 Pt B):E553-8.
10. Santoni M, Conti A, Porta C, et al. Sunitinib, pazopanib or sorafenib for the treatment of patients with late relapsing metastatic renal cell carcinoma. *J Urol.* 2015 Jan;193(1):41-47.
11. Kalra S, Atkinson BJ, Matrana MR, et al. Prognosis of patients with metastatic renal cell carcinoma and pancreatic metastases. *BJU Int.* 2016 May;117(5):761-765.
12. Santoni M, Buti S, Conti A, Porta C, Procopio G, et al. Prognostic significance of host immune status in patients with late relapsing renal cell carcinoma treated with targeted therapy. *Target Oncol.* 2015 Dec; 10(4):517-22.
13. Ha YS, Park YH, Kang SH, Hong SH, Hwang TK, Byun SS, Kim YJ.Predictive factors for late recurrence in patients with stage T1 clear cell renal cell carcinoma: a multiinstitutional study. *Clin Genitourin Cancer.* 2013 Mar;11(1):51-5.
14. Shiono S, Yoshida J, Nishimura M, Nitadori J, Ishii G, Nishiwaki Y, Nagai K. Late pulmonary metastasis of renal cell carcinoma resected 25 years after nephrectomy. *Jpn J Clin Oncol.* 2004 Jan;34(1):46-9.
15. Kucharczyk J, Matrana M. Very late relapse metastatic renal cell carcinoma: Characteristics and outcomes of patients with a disease-free interval of greater than 10 years. Abstract presented at *J Clin Oncol.* 34, no. 2_suppl (January 2016) 541-541. DOI: 10.1200/jco.2016.34.2_suppl.541
16. Carobbio F, Antonelli A, Sodano M, Furlan M, Galvagni G, Cozzoli A, Zanotelli T, Simeone C. How Long Should be Extended Follow up After Surgery for Renal Cancer? Retrospective Analysis of a Cohort of Patients with More than 10 years of Follow-up. *J Urol.* 2015 Apr; 193(4) suppl:e759.
17. Abara E, Chivulescu I, Clerk N, Cano P, Goth A. Recurrent renal cell cancer: 10 years or more after nephrectomy. *Can Urol Assoc J.* 2010 Apr; 4(2): E45–E49. KCJ

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of the CheckMate-214 trial and take into account guidelines from the International mRCC Database Consortium (IMDC). Yes, the combination was superior to sunitinib in patients with intermediate- and poor-risk disease. Notably, however, the schedule modifications of sunitinib, routinely adapted in the general practice and shown to be associated with greater clinical benefit in some patients as compared to the standard 4 weeks ON 2 weeks OFF schedule, were not contemplated in the study. Furthermore, those with favorable risk disease had better results with sunitinib in terms of overall response rate and progression-free survival.

The excitement surrounding immunotherapy may obscure the compelling need to choose the most effective therapy based on evidence for a particular patient at a given time point. For example, how should clinicians consider PD-L1 expression as they contemplate the use of a checkpoint inhibitor? How many of us are mindful of data showing that improvement is likely to be more pronounced in those with tumor PD-L1 expression of 1% or more? What's needed in the calculus is to determine how such markers not only could have an impact on therapeutic choices but on expected outcomes.

These are nuances that are all part of the exciting narrative on treatment selection as we continue to see inflection points in therapy emerge from new data. And they will remain so as the search for predictive biomarkers goes on. Until those biomarkers are revealed, an attempt to administer as many efficacious and reasonably tolerated agents will often be the "default" setting of most clinicians, based on NCCN guidelines, other widely accepted protocols and patient preference. At the same time, the need to drill down and discover the "devil in the details" will help provide an important dimension to clinical decision making and appropriate choices.

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Summary: This ongoing, open-label, phase 1b study, which was done at 10 centers in the US, enrolled patients aged 18 years or older who had advanced RCC (predominantly clear cell) with their primary tumor resected, and at least one measureable lesion, Eastern Cooperative Oncology Group performance status 0-1, controlled hypertension, and no previous systemic therapy for renal cell carcinoma. Axitinib 5 mg was administered orally twice per day with pembrolizumab 2 mg/kg given intravenously every 3 weeks. The primary endpoint was investigator-assessed dose-limiting toxicity during the first two cycles (6 weeks) to estimate the maximum tolerated dose and recommended phase 2 dose. Between Sept 23, 2014, and March 25, 2015, we enrolled 11 patients with previously untreated advanced renal cell carcinoma to the dose-finding phase and between June 3, 2015, and Oct 13, 2015, we enrolled 41 patients to the dose-expansion phase. All 52 patients were analyzed together. No unexpected toxicities were observed. Three dose-limiting toxicities were reported in the 11 patients treated during the 6-week observation period (dose-finding phase): one patient had a transient ischaemic attack and two patients were only able to complete less than 75% of the planned axitinib dose because of treatment-related toxicity. At the data cutoff date (March 31, 2017), 25 (48%) patients were still receiving study treatment. Grade 3 or worse treatment-related adverse events occurred in 34 (65%) patients; the most common included hypertension (n=12 [23%]), diarrhea (n=5 [10%]), fatigue (n=5 [10%]), and increased alanine aminotransferase concentration (n=4 [8%]). The most common potentially immune-related adverse events (probably related to pembrolizumab) included diarrhea (n=15 [29%]), increased alanine aminotransferase concentration (n=9 [17%]) or aspartate aminotransferase concentration (n=7 [13%]), hypothyroidism (n=7 [13%]), and fatigue (n=6 [12%]). 28 (54%) patients had treatment-related serious adverse events. At data cutoff, 38 (73%; 95% CI 59·0-84·4) patients achieved an objective response (complete or partial response).
Conclusion: The treatment combination of axitinib plus pembrolizumab is tolerable and shows promising antitumor activity in patients with treatment-naive advanced RCC. Whether or not the combination works better than a sequence of VEGF pathway inhibition followed by an anti-PD-1 therapy awaits the completion of a phase 3 trial comparing axitinib plus pembrolizumab with sunitinib monotherapy.

A genetic polymorphism in CTLA-4 is associated with overall survival in sunitinib-treated patients with clear cell metastatic renal cell carcinoma. Liu X, Swen JJ, Diekstra MHM, et al. *Clin Cancer Res.* 2018 Feb 28. pii: clincanres.2815.2017. doi: 10.1158/1078-0432.CCR-17-2815.
Summary: With the fact that TKIs interact with immune responses, this report investigated whether polymorphisms of genes involved in immune checkpoints are related to the clinical outcome of cc-mRCC patients treated with sunitinib as first TKI; 27 single nucleotide polymorphisms (SNPs) in CD274 (PD-L1), PDCD1 (PD-1) and CTLA-4 were tested for a possible association with progression-free survival (PFS) and overall survival (OS) in a discovery cohort of 550 sunitinib-treated cc-mRCC patients. SNPs with a significant association (P<0.05) were tested in an independent validation cohort of 138 sunitinib-treated cc-mRCC patients. Finally, data of the discovery and validation cohort were pooled for meta-analysis. CTLA-4 rs231775 and CD274 rs7866740 showed significant associations with OS in the discovery cohort after correction for age, gender and Heng prognostic risk group (HR=0.84, 95%CI: 0.72-0.98, P=0.028 and HR=0.73, 95%CI: 0.54-0.99, P=0.047, respectively). In the validation cohort, the associations of both SNPs with OS did not meet the significance threshold of p<0.05. After meta-analysis, CTLA-4 rs231775 showed a significant association with OS (HR=0.83, 95%CI: 0.72-0.95, P=0.008). Patients with the GG-genotype had longer OS (35.1 months) compared to patients with an AG (30.3 months) or AA genotype (24.3 months). No significant associations with PFS were found.
Conclusion: The G-allele of rs231775 in the CTLA-4 gene is associated with improved OS in sunitinib-treated cc-mRCC patients and could potentially be used as a prognostic biomarker.

Randomized phase III trial of adjuvant pazopanib versus placebo after nephrectomy in patients with localized or locally advanced renal cell carcinoma. Motzer RJ, Haas NB, Donskov F, et al. *J Clin Oncol.* 2017 Dec 10;35(35):3916-3923. doi: 10.1200/JCO.2017.73.5324. Epub 2017 Sep 13.
Summary: This phase III trial evaluated the efficacy and safety of pazopanib vs placebo in patients with locally advanced RCC at high risk for relapse after nephrectomy. A total of 1,538 patients with resected pT2 (high grade) or ≥pT3, including N1, clear cell RCC were randomly assigned to pazopanib or placebo for 1 year; 403 patients received a starting dose of 800 mg or placebo. To address toxicity attrition, the 800-mg starting dose was lowered to 600 mg, and the primary end point analysis was changed to disease-free survival (DFS) for pazopanib 600 mg versus placebo (n = 1,135). Primary analysis was performed after 350 DFS events in the intent-to-treat (ITT) pazopanib 600 mg group (ITT600mg), and DFS follow-up analysis was performed 12 months later. Secondary end point analyses included DFS with ITT pazopanib 800 mg (ITT800mg) and safety. The primary analysis results of DFS ITT600mg favored pazopanib but did not show a significant improvement over placebo (P = .165). The secondary analysis of DFS in ITT800mg (n = 403) yielded an HR of 0.69 (95% CI, 0.51 to 0.94). Increased ALT and AST were common adverse events leading to treatment discontinuation in the pazopanib 600 mg (ALT, 16%; AST, 5%) and 800 mg (ALT, 18%; AST, 7%) groups.
Conclusion: The results of the primary DFS analysis of pazopanib 600 mg showed no benefit over placebo in the adjuvant setting. KCJ

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IMmotion150 is the first randomized clinical trial to evaluate the combination of atezolizumab and bevacizumab in advanced RCC. The study was designed to inform further clinical development of this combination, and these study results reinforce the potential of the combination in this setting.

Patients whose disease expressed programmed cell death ligand 1 (PD-L1) and were treated with atezolizumab plus bevacizumab had a 36% reduction in the risk of the disease worsening or death compared to people treated with sunitinib alone (median progression-free survival = 14.7 vs 7.8 months; hazard ratio [HR] = 0.64; 95% confidence interval [CI] = 0.38–1.08). No progression-free survival advantage was observed compared to sunitinib in the intention-to-treat population (median = 11.7 vs 8.4 months; HR = 1.00; 95% CI = 0.69–1.45).

Median duration of response has not yet been reached after 20.7 months of follow-up across treatment arms. Adverse events in the atezolizumab-plus-bevacizumab arm were consistent with those observed in previous studies of each drug.

First-line Pazopanib May Improve Outcomes in Advanced RCC

PFS among patients with intermediate-risk advanced clear-cell renal cell carcinoma (aCCRCC) is significantly longer with pazopanib than temsirolimus as first-line therapy, according to the findings of a randomized phase II clinical trial presented at the 2018 Genitourinary Cancers Symposium. Pazopanib therapy also appeared to elicit a better objective response rate (ORR). Median PFS, the study's primary end point, was 5.2 months (95% CI 3.6–7.4) for pazopanib compared with 2.6 months (95% CI 1.9–4.2) for temsirolimus, Nizar M. Tannir, MD, and colleagues at the University of Texas Health Science Center at Houston reported. Among patients with intermediate-risk disease as defined by International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria, pazopanib was associated with a significant 62% decreased risk of progression compared with temsirolimus The median overall survival was 12 months (95% CI 8.3–20.1) for the pazopanib group and 7.4 months (95% CI 5.3–17.4) for the temsirolimus group. The study found no significant difference between the drugs among patients in the IMDC poor-risk group.

Phase 3 Trial Design Outlined for Lenvatinib in Combination with Everolimus or Pembrolizumab vs Sunitinib

Investigators reviewed the design of a multicenter, open-label, phase 3 trial of lenvatinib plus everolimus or pembrolizumab vs sunitinib as first-line treatment for advanced RCC. Patients will be randomized 1:1:1 to receive LEN 18 mg/d + EVE 5 mg/d, LEN 20 mg/d + PEM 200 mg every 3 weeks, or SUN 50 mg/d (on a schedule of 4 weeks on treatment followed by 2 weeks off) until disease progression, unacceptable toxicity, withdrawal of consent, or study end. Enrollment of 735 patients is planned.

The primary endpoint is to assess superiority of LEN+EVE or LEN+PEM over single-agent SUN as first-line treatment for advanced RCC in improving progression-free survival (PFS) The secondary endpoints: comparison of objective response rate (ORR), overall survival, PFS on next-line therapy, health-related quality of life, and safety and tolerability in pts receiving LEN+EVE or LEN+PEM vs SUN.

Exploratory endpoints: PFS in the LEN+PEM arm using immune-related RECIST, comparison of duration of response, disease control rate, and clinical benefit rate in pts treated with LEN+EVE or LEN+PEM vs SUN, and analysis of the relationship between blood biomarkers and outcome. KCJ

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