Volume 15, Number 2 2017

Kidney Cancer JOURNAL

Official Journal of The Kidney Cancer Association

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Identifying and Managing a Spectrum of Toxicities

- Multi-organ involvement
- Data on checkpoint inhibitors, targeted therapy
- A case report on osteonecrosis of the jaw

Plus: A Special Report on Highlights from ASCO 2017

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

Now in Its 15th Year

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

Important Safety Information

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

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

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

Cardiac failure has been observed and can be fatal. Monitor for signs or symptoms of cardiac failure throughout treatment with INLYTA. Management of cardiac failure may require permanent discontinuation of INLYTA.

Gastrointestinal perforation and fistula, including death, have occurred. Use with caution in patients at risk for gastrointestinal perforation or fistula. Monitor for symptoms of gastrointestinal perforation or fistula periodically throughout treatment.

Hypothyroidism requiring thyroid hormone replacement has been reported. Monitor thyroid function before initiation of, and periodically throughout, treatment.

No formal studies of the effect of INLYTA on **wound healing** have been conducted. Stop INLYTA at least 24 hours prior to scheduled surgery.

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

Inlyta®
axitinib 1mg and 5mg tablets

Continue the fight with INLYTA

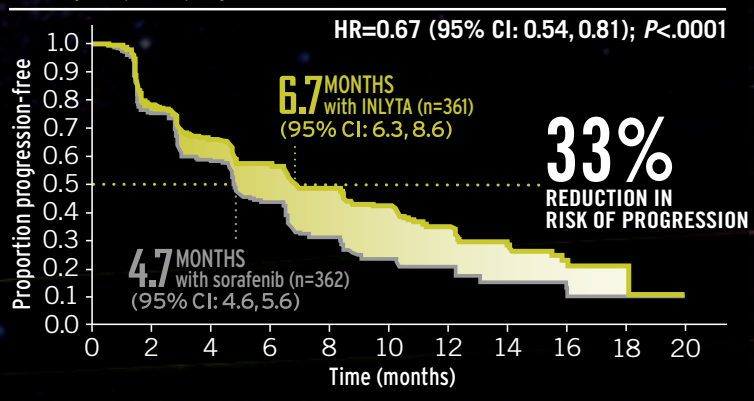
Proven efficacy with a distinct safety profile

The ONLY approved treatment option to demonstrate

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

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

Primary endpoint: progression-free survival (PFS)



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

A distinct safety profile

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

†IMS® MIDAS™, July 2016.

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

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

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

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

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

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

The **most common (≥20%) adverse events (AEs)** occurring in patients receiving INLYTA (all grades, vs sorafenib) were diarrhea (55% vs 53%), hypertension (40% vs 29%), fatigue (39% vs 32%), decreased appetite (34% vs 29%), nausea (32% vs 22%), dysphonia (31% vs 14%), hand-foot syndrome (27% vs 51%), weight decreased (25% vs 21%), vomiting (24% vs 17%), asthenia (21% vs 14%), and constipation (20% vs 20%).

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

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

Please see Brief Summary on the following pages.

November 2016

Pfizer U.S. Pharmaceuticals

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

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

Brief Summary of Prescribing Information

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

DOSAGE AND ADMINISTRATION

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

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

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

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

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

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

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

DOSAGE FORMS AND STRENGTHS

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

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

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DRUG INTERACTIONS

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

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

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

USE IN SPECIFIC POPULATIONS

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

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

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

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

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

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

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

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

No dosage adjustment is required in elderly patients.

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

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

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

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

OVERDOSAGE

There is no specific treatment for INLYTA overdose.

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

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

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

NONCLINICAL TOXICOLOGY

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

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

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

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

PATIENT COUNSELING INFORMATION

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

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

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

Rx only August 2014

About the Cover
A broad spectrum of toxicities may be associated with various treatments for renal cell carcinoma. The figures in this illustration represent possible multi-organ involvement and potential adverse reactions related to treatments that include immunotherapy and targeted therapy. Reports in this issue suggest how these toxicities can be managed and the safety profile of agents can be optimized. (Copyright ©, Carol and Mike Werner / Science Source)

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KCJ EDITOR'S MEMO

Following the Foot Prints Left by ASCO 2017: Reflections and Observations

As the ASCO Scientific Sessions of 2017 recede on our calendars, what will be our "take-home" messages? Will we see these sessions in much the same way we view objects in the rear view mirror of our vehicle, as "closer than they actually appear"? In other words, we might speculate as to how close we are to approaching the time when trends observed at ASCO actually have translational impact on our practices.

Much of this is already happening, so don't look now, but your practice is changing as we speak, and what we see retrospectively from ASCO is already having a sharp impact on how we treat RCC. Here are some quick snapshots from the meeting and general observations:

Adjuvant therapy. We know that a recent *New England Journal of Medicine* article demonstrated that sunitinib prolongs progression-free survival (PFS) when compared to placebo in high risk, resected patients. The PROTECT trial, as reported at ASCO demonstrated the intent-to-treat analysis was negative but patients who received pazopanib at full doses showed a hazard ratio significantly less than placebo. This suggests that we may need to give targeted agents at full doses in the adjuvant setting to achieve the full impact.

Landscape of treatment. We have a series of drugs available for sequencing—there are TKIs, followed by immune-oncology (IO). Clearly, there are trials that continue to change the landscape. For example, CABOSUN is a trial that compared cabozantinib and sunitinib in the frontline setting with some demonstrated benefit with respect to PFS and OS. If cabozantinib receives regulatory approval, that might change the landscape. The upfront IO combinations or IOs and targeted therapies as illustrated at the 2017 ASCO meeting will be the kinds of trials that will change the landscape in the future.

Immuno-oncology. As we understand the interaction between cancer and the immune system, we recognize that single checkpoint inhibitors have great efficacy, but probably combinations are better, whether it's IO-IO, or IO and targeted therapy or IO and a novel therapy. In 5 years we will look back and say that the 1990s and 2000s were the era of targeted therapy, but beyond that we are likely to say that IOs are a better replacement.

Sequencing of therapy. In the frontline, the targeted agent could be pazopanib or sunitinib or a clinical trial. In the second line we have much controversy because we have a series of drugs, many of which have demonstrated both progression-free and overall survival benefits compared to mTOR inhibitors but have never been compared to each other. In my practice, I tend to use nivolumab first as the second line therapy because I am trying to obtain that tail of the curve and an improvement in overall survival. I reserve agents like cabozantinib and everolimus but that may change depending on how the

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Kidney Cancer Journal Author Guidelines

Scope of Manuscripts

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

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

Manuscript Submission

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

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Contact information

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

Peer Review and Editing

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

Conflict of Interest

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

Manuscript Preparation

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

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

References

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

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Essential Peer-Reviewed Reading in Kidney Cancer

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

Systemic Therapy for non-clear cell renal cell carcinoma. Zhang T, Gong J, Maia MC, et al. *Am Soc Clin Oncol Educ Book*. 2017; 37:337-342.

Summary: Little improvement has been made in the management of metastatic non-clear cell RCC (nccRCC). Non-clear cell disease is an umbrella term that encompasses multiple biologically distinct entities, including but not limited to papillary, chromophobe, and sarcomatoid RCC. To date, prospective studies have largely explored treatments for ccRCC (e.g., VEGF- and mTOR-directed therapies) in trials that aggregate non-clear cell histologies. However, the studies do not acknowledge the varying biology of each non-clear cell subtype.
Conclusion: Emerging studies in nccRCC should examine individual histologies and apply biologically relevant therapies. An example of this is SWOG 1500, a randomized phase II study that will compare a VEGF-inhibitor to one of three MET-directed therapies in patients with metastatic papillary RCC. Until the biologic diversity of nccRCC is appreciated, outcomes are likely to remain dismal.

Metastatic chromophobe renal cell carcinoma treated with targeted therapies: A Renal Cross Channel Group study. Colomba E, Le Teuff G, Eisen T, et al. *Eur J Cancer*. 2017; 23;80:55-62

Summary: Treatment of non-clear cell renal cell carcinoma (RCC) remains controversial despite several recent prospective studies of targeted therapies (TT). Often Vascular Endothelial growth Factor (VEGF) and Mammalian Target of Rapamycin (mTOR) inhibitors are used, extrapolating the data from use of these agents in clear cell RCC. This study performed a retrospective data analysis within the Renal Cross Channel Group to determine metastatic chromophobe RCC (mChRCC) outcomes in the TT era. The end-points were overall response, overall survival (OS) and time to treatment failure (TTF). The two latter were estimated using the Kaplan-Meier method. The study included 91 mChRCC patients from 26 centers. Median follow-up from the date of first metastasis was 6.1 years (range: 0-13.9). Median OS was 37.9 months from the diagnosis of metastatic disease. Among the 61 patients who received TT, 50 (82%) were treated with anti-angiogenic (AA) and 11 with mTOR inhibitors. Median TTF and OS in patients receiving a first line of AA was 8.7 months and 22.9 months vs 1.9 months and 3.2 months with mTOR inhibitors, respectively. A stratified log-rank test compared AA and mTOR inhibitors TT, while controlling the effect of the International Metastatic RCC Database Consortium risk group and no significant difference between AA and mTOR inhibitors was observed for TTF ($P = 0.26$) or for OS ($P = 0.55$).
Conclusion: This report, the largest retrospective cohort of patients with mChRCC treated with TT, found no significant difference between AA and mTOR inhibitors for TTF and OS.

Collecting duct carcinoma of the kidney: Disease characteristics and treatment outcomes from the National Cancer Database. Sui W, Matulay JT, Robins DJ, et al. *Urol Oncol*. 2017 May 8; pii: S1078-1439(17)30179-5.

Summary: The National Cancer Database was queried for all cases of CDRCC and clear cell renal cell carcinoma (CCRCC) from 2004 to 2013. After removing patients with other cancer diagnoses, the analytic cohort was composed of 201,686 CCRCC and 577 CDRCC cases. Kaplan-Meier and cox proportional hazards analysis were employed to model survival. Compared to CCRCC, patients with CDRCC presented with higher grade stage, node positive, and metastatic disease (70.7% vs. 30.0% with metastasis; $P<0.001$). Overall median survival for CDRCC was 13.2 months for CCRCC. Increasing T stage, high-grade disease, and metastasis were predictors of mortality. Of 184 patients with metastatic CDRCC, 113 underwent cytoreductive nephrectomy (CNx) whereas the rest were treated with chemo/radiation or observed. Survival outcomes were improved in patients who received both CNx with chemo/radiation compared to CNx alone or chemo/radiation alone.
Conclusion: CDRCC is an aggressive subtype of RCC. Median survival is 13 months after diagnosis, drastically lower than for CCRCC. More than 70% of patients have a metastatic disease at diagnosis. Chemo/radiation in addition to CNx is associated with a survival benefit over single mode therapy.

Multicenter evaluation of the tolerability of combined treatment with PD-1 and CTLA-4 immune checkpoint inhibitors and palliative radiation therapy. Bang A, Whilhite TJ, Pike LRG, et al. *Int J Radiat Oncol Biol Phys*. 2017 Jun 1;98(2):344-351.

Summary: Records from patients with metastatic non-small cell lung cancer, melanoma, or renal cell cancer who received at least 1 cycle of a CTLA-4 or PD-1 inhibitor and radiation were retrospectively reviewed. Immune-related adverse events, defined using Common Terminology Criteria for Adverse Events version 4.0, were tabulated in relation to treatment variables, and associations with

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

New results from CABOSUN, phase 2 trial of cabozantinib vs sunitinib in previously untreated advanced renal cell carcinoma

- **IRC confirms cabozantinib significantly improved progression-free survival compared to sunitinib**
- **US regulatory submission remains on track for Q3'17**

SOUTH SAN FRANCISCO, CA— Exelixis, Inc. has announced that the analysis of the review by a blinded independent radiology review committee (IRC) confirmed the primary efficacy endpoint results of investigator-assessed progression-free survival (PFS) from the CABOSUN randomized phase 2 trial. This trial compares cabozantinib with sunitinib in patients with previously untreated advanced renal cell carcinoma (RCC) with intermediate- or poor-risk disease per the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC). Per the IRC analysis, cabozantinib demonstrated a clinically meaningful and statistically significant reduction in the rate of disease progression or death as measured by PFS. Exelixis remains on target to complete a supplemental New Drug Application (sNDA) for cabozantinib as a treatment of first-line advanced renal cell carcinoma in the third quarter of 2017.

CABOSUN was conducted by The Alliance for Clinical Trials in Oncology as part of Exelixis' agreement with the National Cancer Institute's Cancer Therapy Evaluation Program (NCI-CTEP). Exelixis and the Alliance cooperative group plan to submit these results for presentation at an upcoming international medical meeting.

Calithera Biosciences announces FDA fast track designation granted to CB-839 for renal cell carcinoma

SOUTH SAN FRANCISCO, CA—Calithera Biosciences, Inc., a clinical stage biotechnology company focused on the development of novel cancer therapeutics, today announced that the U.S. Food and Drug Administration (FDA) has granted Fast Track designation to CB-839 in combination with everolimus, for the treatment of patients with metastatic renal cell carcinoma (RCC) who have received 2 or more prior lines of therapy. CB-839 is a first-in-class, oral, selective, potent inhibitor of glutaminase being evaluated in Phase 1/2 clinical trials for the treatment of solid tumors including RCC, triple negative breast cancer, non-small cell lung cancer, and melanoma.

The FDA's Fast Track designation is designed to facilitate the development and expedite the review of drugs and biologics, to treat serious or life threatening conditions, and to fill an unmet medical need. Specifically, Fast Track designation facilitates frequent interactions with the FDA review team, including meetings to discuss all aspects of development to support approval, and also provides the opportunity to submit sections of an NDA on a rolling basis as data become available.

AVEO Oncology announces phase 1/2 TiNivo trial of tivozanib and Opdivo® (nivolumab) in RCC advances to phase 2

CAMBRIDGE, MA—AVEO Oncology announced that its Phase 1/2 AVEO-sponsored TiNivo trial evaluating tivozanib in combination with Bristol-Myers Squibb's anti-PD-1 therapy, Opdivo® (nivolumab), in subjects with advanced renal cell carcinoma (RCC) has progressed to the Phase 2 portion of the trial.

Advancement of the study into the Phase 2 expansion follows the successful completion of the Phase 1 dose escalation portion of the trial, where tivozanib was administered in two escalating dose cohorts in combination with nivolumab at a constant 240 mg every 2 weeks (n=6). The combination was well tolerated to the full dose and schedule of single agent tivozanib, with no dose limiting toxicities. The full dose tivozanib regimen of 1.5 mg daily for 21 days, followed by a 7 day rest period, is the recommended Phase 2 dose (RP2D) for the expansion portion of the trial, which is expected to enroll up to an additional 20 subjects. The TiNivo study is being led by the Institut Gustave Roussy in Paris under the direction of Bernard Escudier, MD, Chairman of the Genitourinary Oncology Committee. Phase 1 results from the ongoing study will be submitted for presentation at an upcoming scientific meeting.

"The promise of delivering synergistic activity by combining VEGF TKIs and PD-1s in renal cell carcinoma hinges on the tolerability of the combination," said Dr. Escudier. "Tivozanib has a uniquely favorable tolerability profile as demonstrated in past single agent and combination studies. These initial results are very promising in that we see both evidence of a uniquely tolerable combination as well as early and meaningful activity. I look forward to enrolling the expansion cohort and to establishing a broader understanding for the potential of this compelling combination."

"Together with the longest progression free survival from a Phase 3 first line RCC study, tivozanib's tolerability is distinct from other VEGF TKIs, which we believe better position it for use in combination with immunotherapy and other agents," said Michael Bailey, president and chief executive officer of AVEO. "As our registration strategy for single agent tivozanib reaches key inflection points, with a European regulatory decision expected in the near-term and readout of our US registration-directed TIVO-3 study expected in the first quarter of 2018, our attention is increasing on tivozanib immuno-oncology combinations that have the potential to deliver significantly improved outcomes and tolerability to patients. The TiNivo trial is an important first step in this effort, and we share Dr Escudier's enthusiasm for the completion of this trial." KCJ

Optimizing the Safety Profile of Immune Checkpoint Blockade in Renal Cell Carcinoma

Martin H. Voss, MD
Assistant Attending
Department of Medicine
Memorial Sloan Kettering Cancer Center
New York, New York

In this review, current information on the diagnosis, monitoring, and management of immune-related adverse reactions of anti-PD-1 antibody therapy is presented. Recent literature highlights optimal strategies for managing specific adverse events related to antibodies that target this pathway.

In only a few years immune checkpoint blockade has rapidly moved from the bench to a transformative position in cancer therapy, and by 2017, molecularly targeted immunotherapeutics directed against Programmed Death 1 (PD1), its ligand PD-L1 and Cytotoxic T-Lymphocyte-Associated protein 4 (CTLA4) have become an approved standard across a number of solid tumor malignancies, including melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), bladder cancer and head and neck cancer.

This new generation of drugs augments cancer-directed immune response of the host by modulating the effects of regulatory surface receptors on human immune cells, so-called immune checkpoints. Through activation of cancer-antigen specific T effector cells these agents can achieve powerful anti-cancer effect and induce long-lasting treatment responses. A growing list of targets is being explored in the treatment of RCC. The PD-1 directed humanized monoclonal antibody nivolumab is FDA approved for the treatment of tyrosine kinase inhibitor (TKI) pretreated advanced RCC.

Exploiting function of immune regulators therapeutically can lead to treatment induced adverse events (AE) via immune-activation and resulting inflammatory changes in healthy tissues. Immune-related adverse events (irAEs) can affect any organ system, most commonly the skin, gastrointestinal, hepatic, and endocrine systems. Early data suggest that temporary use of immunosuppressive medications administered to suppress these side effects does not eliminate the possibility of a favorable antitumor effect. Our review of current literature offers important perspectives from which to explore the principles of immune-related adverse events recognition and management. These are increasingly important considerations beyond kidney cancer as the use of these antibodies expands. Although guidelines are emerging on the optimal management of irAEs, there is a relative scarcity of prospective trials on evaluating the best treatment approaches to manage these unique side effects.

Treatment Administration and Safety: The Pivotal Nivolumab Study

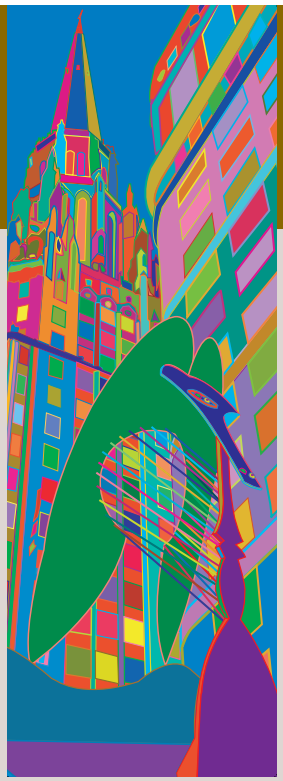
The phase 3 CheckMate 025study reported by Motzer et al[1] established the benefits of nivolumab for RCC and delineated the safety profile of this agent in the largest cohort reported to date. It showed that patients with advanced RCC who had received previous antiangiogenic treatment achieved longer overall survival (OS) with nivolumab treatment than with everolimus treatment. The separation of the OS curves occurred early in the study, and there was a 5.4 months absolute difference in median OS with nivolumab than with everolimus (25.0 months vs. 19.6 months), a difference that crossed the prespecified boundary for significance at the time of the interim analysis.[1]

The median duration of treatment was 5.5 months (range, <0.1 to 29.6) with nivolumab and 3.7 months (range, 0.2 to 25.7) with everolimus. While the protocol did not allow dose reductions for AEs, 51% patients treated with nivolumab (51%) had at least one dose delay, and 66% patients treated with everolimus (66%) had dose delays (including interruptions). A total of 102 of the 397 patients in the everolimus group (26%) had at least one dose reduction.

The authors reported that treatment-related adverse events of any grade occurred in 79%of patients treated

Keywords: Immune checkpoint blockade, immune-related adverse events, PD1, PD-L1, nivolumab, dermatologic, hepatic, endocrinopathy, diarrhea, colitis, pneumonitis.

Address for reprints and correspondence: Martin H. Voss, MD, Memorial Sloan Kettering Cancer Center, 1275 York Ave., New York, NY, 10065. Email: vossm@mskcc.org



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with nivolumab versus 88% of those having received everolimus. The most common treatment-related adverse events with nivolumab were fatigue (134 patients, 33%), nausea (57 patients, 14%), and pruritus (57 patients, 14%); among patients who received everolimus, the most common events were fatigue (134 patients, 34%), stomatitis (117 patients, 29%), and anemia (94 patients, 24%). Grade 3 or 4 treatment-related adverse events occurred in 19% and 37% of patient treated with nivolumab and everolimus, respectively; the most common grade 3 or grade 4 event was fatigue (10 patients, 2%) with nivolumab.[1]

Treatment-related adverse events leading to treatment discontinuation occurred in 8% of patients treated with nivolumab and in 13% of patients treated with everolimus. No deaths from study-drug toxic effects were reported in the nivolumab group, and two deaths were reported in the everolimus group (one from septic shock and one from acute bowel ischemia).

In a subsequent presentation the authors reported on the timing of onset and resolution of select AEs, addressing the unique nature of immune-mediated toxicties.[2] While the median time to onset was <12wks for hepatic, skin, GI, renal irAEs, it tended to be later in immune endocrinopathies (median 16.4 weeks) and pneumonitis (median 17.4 weeks). Notably, the range of symptom onset was wide for each organ, several patients developing irAEs >100 weeks into treatment.[2] Similarly, time to resolution of AE varied greatly across patients with some subject for all reported AEs requiring >1y until reported resolution. Importantly, the primary publication for Checkmate025 provided no details on the management of irAEs beyond the general rate of dose delays and treatment discontinuations. On the dose-randomized phase II study of nivolumab in metastatic RCC the rate of giving systemic corticosteroids for the management of AEs (regardless of causality) was 15-33% across three different dosing groups.[3]

This can be put in context with data from patients with advanced melanoma treated on clinical trials. Weber et al. reported on over 500 patients treated with single agent nivolumab across four trials.[4] The authors found that the kinetics of onset and resolution of irAEs varied with distinct patterns across different organ systems, e.g. hepatic, skin and gastrointestinal toxicity emerging earlier, renal toxicity later. While many of these lingered for extended periods of time, no new-onset treatment related AEs were documented in patients 80 weeks or longer on therapy.[4] Similarly, McDermott et al. recently presented long-term outcomes for RCC patients who received nivolumab on one other original phase I and phase II monotherapy studies. No new-onset irAEs across organ domains of interest (endocrine, gastrointestinal, hepatic, pulmonary, renal, and skin) were recorded beyond 30 months from treatment start.[5] Such data suggest that organ-specific immune toxifies can be delayed and in some patients persist for extended periods of time; however, they are unlikely to newly develop late in the course of those patients who have achieved extended benefit from therapy.

In the above cited report for nivolumab-treated melanoma patients,[4] 24% of subjects received systemic immunomodulatory (IM) drugs to treat adverse effects. This was not associated with an apparent loss in treatment benefit, the objective response rate being 29.8% in IM-treated patients vs. 31.8% in others. In fact, adjusting for number of doses, response rate was higher in patients who experienced treatment related AEs in this dataset.

These findings add to a growing body of safety data collected on studies performed in other diseases using this class of agents. Eigentler et al[6] reviewed pooled data from pivotal trials, conducted not only in advanced RCC but also melanoma and non-small-cell lung cancer (NSCLC) as reported by the European Medicines Agency. The authors scrutinized incidence and kinetics of onset and resolution of immune-mediated "adverse events of specific interest" (AEOSI) for the two PD-1 inhibitors nivolumab and pembrolizumab. They found that the severity of AEOSI was generally mild to moderate (grade 1–2); the frequency of grade 3–4 adverse drug reactions was rarely >2% for any event term, the exception being grade 3 fatigue which was reported in >2% of patients in NSCLC and RCC. The onset of irAEs was highly variable across organ systems and underlying malignancies.

On further analysis, the authors made recommendations for the diagnosis, monitoring and management of relevant dermatological, gastrointestinal, pulmonary, endocrine, renal and hepatic toxicities, including the use of topical and systemic corticosteroids as well as non-steroidal immunosuppressants.

Most Common Types of Immune-Related Adverse Events

Dermatologic events. Dermatologic toxicity is among the most common adverse events and typically observed to have early onset; 10% of patients developed treatment-related rashes with nivolumab on CheckMate 025 with median onset at 8.4 weeks.[2] With checkpoint blockade, the sign of an adverse event is most likely to emerge as a faintly erythematous rash. Reticular and maculopapular, it is generally observed on the trunk and extremities.[6] The incidence of pruritus is similarly high (14% of patients on CheckMate 025), often presenting is an isolated symptom without rash.

The initial approach for dermatologic toxic effects is supportive. Topical corticosteroid creams of medium to high potency can be used for rash.[7] Cold compresses, oatmeal baths, and topical corticosteroids may be helpful in relieving symptoms of pruritus in addition to systemic antihistamines such as diphenhydramine hydrochloride and hydroxyzine hydrochloride. Oral or topical doxepin hydrochloride, a tricyclic antidepressant, has also been used with some success for pruritic symptoms as has oral aprepitant.[7] Anti–CTLA-4 or anti–PD-1 therapy can be continued while managing grade 1 to 2 skin toxic effects. Severe rash (grade 3 or higher) should be treated with sys-

temic corticosteroids, usually at an equivalent dose of prednisone 1-mg/kg daily.

In such cases, treatment checkpoint inhibitor therapy should be interrupted until symptoms improve to baseline or grade 1 or lower before more treatment can be considered. In the event of severe rashes, not responsive to oral corticosteroids, clinicians should consider dermatology consultation and the addition of immunosuppressive medications such as infliximab, mycophenolate mofetil, or cyclophosphamide. Treatment with immune checkpoint inhibitors should be permanently discontinued if cutaneous symptoms fail to improve after 12 weeks of supportive management due to the risk of more severe symptoms.

Diarrhea/colitis. Diarrhea/colitis with CTLA-4 blockade is more common than with PD-1/PD-L1 blockade. The rate of grade 3/4 diarrhea in patients treated with PD-1/PD-L1 agents is very low across diseases, including RCC where treatment related diarrhea with nivolumab was reported in 12%, but only 1% grade ¾. For any patient with treatment-emergent diarrhea, clinicians should consider other etiologies that may be responsible, such as *Clostridium difficile* infection or other bacterial/viral pathogens. Patients should be counseled on the importance of maintaining oral hydration. Some clinicians find that the American Dietary Association's colitis diet and antimotility agents (oral diphenoxylate HCl and atropine sulfate 4 times a day) can be helpful. For persistent mild diarrhea the use of oral budesonide can be considered (see below). For patients with symptoms refractory to these interventions, and for those with grade 3 diarrhea and negative infectious workup the use of oral or intravenous corticosteroids is required.[8]

When symptoms are refractory to oral corticosteroids, hospitalization for intravenous corticosteroids, hydration, and electrolyte management is required. Endoscopic workup can be reserved for situations when the diagnosis is unclear. If intravenous corticosteroids (up to 2 mg/kg methylprednisolone twice a day) do not lead to symptom resolution, infliximab (Remicade; Janssen Biotech, Horsham, PA) at a dose of 5 mg/kg, once every 2 weeks can be effective in patients with steroid-refractory colitis.[9-11] The use of infliximab in this setting is based on its use in patients with inflammatory bowel diseases.[12] In very rare cases, colitis can result in bowel perforation and require surgical intervention, and in some cases colostomy.

In patients with low-grade events and those with prompt response to immunosuppressive therapy, anti-PD-1 therapy may be resumed after glucocorticoid taper, which should be carried out over at least 1 month to prevent symptom rebound. In high-grade and steroid-refractory cases, therapy must be permanently discontinued.[12,13] Unfortunately, there are no proven treatments to prevent the occurrence of diarrhea. In one study, prophylactic use of the matrix-release corticosteroid budesonide was not found to be helpful.[14]

Hepatic events. Hepatitis, as determined by elevations in aspartate aminotransferase (AST), aminotransferase (ALT) and less commonly, total bilirubin, can develop in patients treated with checkpoint blockade. Although most episodes present only as asymptomatic laboratory abnormalities, some patients have an associated fever. Rates of AST and ALT elevations with CTLA-4 blockade vary among clinical trials, but they typically have been reported in less than 10% of patients.[15] In large trials of PD-1–blocking antibodies, the rates of hepatitis were lower(below 5%) and grade ¾ toxicity was even less common.[11,12] On the RCC registration trial the rate of immune-related hepatitis was low (1.5%, and early in onset (median 7.3 weeks) reference.[2]

Radiographic findings are not typical. In severe cases, however, findings on CT scans may include mild hepatomegaly, periportal edema, or periportal lymphadenopathy.[14] Liver biopsies have described pathologic changes that include severe panlobular hepatitis with prominent perivenular infiltrate with endothelialitis or a primary biliary pattern with mild portal mononuclear infiltrate around bile ductules.[14,16]

Hepatic function (transaminases and bilirubin) should be monitored before each dose of checkpoint inhibitor therapy. In the setting of rising transaminases, viral and other drug-induced causes of hepatitis should be excluded. Patients with grade 1 elevations may not need treatment-interruption, but should we closely monitored for further enzyme rise, e.g. with once-twice weekly blood draws. For patients with grade ≥2 events treatment should be interrupted, alternative etiologies should be investigated, and prompt treatment with systemic corticosteroids is advised (e.g. starting dose prednisone 1mg/kg QD or equivalent) with close monitoring of liver function, ideally daily blood draws. Typically, responses are swift Once liver function tests have improved to within grade 1, steroids can be tapered, typically over a minimum of 3-4 weeks. In rare cases, elevations in AST and ALT are steroid-refractory and 500 mg every 12 hours of mycophenolate mofetil (CellCept; Genentech, South San Francisco, CA) may be helpful. The use of antithymocyte globulin therapy also was described in a case report.[8] Unlike for patients with diarrhea/colitis, infliximab should not be given to patients with hepatitis because infliximab carries a risk of hepatotoxicity.

Endocrinopathy. Immune-related adverse events that affect the pituitary, adrenal, and thyroid glands often present with nonspecific symptoms such as nausea, headache, and fatigue.[8] Despite difficulties in determining the incidence of such AEs—due to the variable methods of assessment, diagnosis, and monitoring in each clinical trial, new data are emerging. For example, hypophysitis (pituitary inflammation) and hypothyroidism are the most common endocrinopathies and reportedly occur in up to 10% of patients treated with CTLA-4 blockade.[8]

The most frequent AE is thyroid dysfunction, which is seen in approximately 10% of RCC patients receiving

nivolumab[17]; typically, a transient period of subclinical hyperthyroidism proceeds a drop in function, ultimately requiring thyroid replacement therapy. A report of lung cancer patients treated with the PD1 inhibitor pembrolizumab recently reported that many patients with new thyroid dysfunction developed new thyroid antibodies.[18]Development of isolated thyroid dysfunction does not require initiation of systemic corticosteroids in addition to thyroid replacement therapy.

Immune mediated hypophysitis is the most feared endocrinopathy, in which all hormones released by the pituitary may be reduced simultaneously (adrenocorticotropic hormone [ACTH], thyroid stimulating hormone [TSH], follicle stimulating hormone, luteinizing hormone, growth hormone, prolactin). Typically, hypophysitis presents with headache, skin and constitu- tional changes, labile blood pressure, clinical hypogonadism and general malaise. Laboratory abnormalities include hyponatremia, secondary hypothyroidism, low ACTH and gonadotropins and sex hormones. A sellar MRI should be obtained which typically reveals inflammatory sequelae with enhancement and enlargement of the pituitary gland itself[19,20] (low ACTH and TSH). Biochemical tests associated with hypophysitis are distinct from primary adrenal insufficiency (low cortisol or inappropriate cortisol stimulation test; high ACTH) and primary hypothyroidism (low free T4; high TSH).

If hypophysitis is suspected, anecdotal reports suggest that a course of high-dose corticosteroids (1 mg/kg of prednisone daily) given during the acute phase can reverse the inflammatory process and prevent the need for longer-term hormone replacement.[21] In almost all patients, however, longer-term supplementation of affected hormones is necessary because of secondary hypothyroidism (treated with levothyroxine) or secondary hypoadrenalism (treated with replacement doses of hydrocortisone, typically 20 mg each morning and 10 mg each evening). Some authors have described that patients can be successfully weaned from replacement corticosteroids over time, but this is likely the exception.[21] The immunologic mechanisms of hypophysitis are unknown, but they may be related to the development of humoral (antibody) immunity against the pituitary gland and subsequent complement activation.[22] Urgent care for endocrinopathy is warranted when an adrenal crisis associated with dehydration, hypotension, and electrolyte imbalances such as hyperkalemia and hyponatremia occur.

In this event, patients need to be hospitalized with intravenous corticosteroids administered. Consultation with an endocrinologist, aggressive hydration, and evaluation for sepsis is critical.

For many patients the presentation is subclinical: Since routine monitoring of thyroid function tests (TSH) is frequently performed by oncologists, patients often are diagnosed with thyroid abnormalities (hyperthyroidism and hypothyroidism) as a result of checkpoint blockade. oxine).

Hypophysitis rarely has been described in published trials of PD-1 blockade for patients with advanced melanoma.[9,11] and was reported in only 0.5% of patients receiving niviolumab on the RCC registration trial. [17]

Pneumonitis. There is a broad spectrum of less common AEs associated with checkpoint blockade; although they are rare, the toxicities may take the form of pancreatitis, hematologic AEs, neurologic events, pneumonitis, and nephritis. Pneumonitis is of particular concern because it may worsen despite immunosuppression and may result in infection and/or death. In RCC pneumonitis was reported in 4.4% of patients receiving nivolumab on the pivotal trial,[17] high grade pneumonitis was only seen in 1% of patients.[1]

A report by Naidoo et al[24] is noteworthy because it is a relatively large study and the clinical experience of patients with anti-PD-1/PD-L1 associated pneumonitis has not been comprehensively described. The study also addresses another gap in the literature because management and outcomes have not been thoroughly addressed. Naidoo described the clinical, radiologic, and pathologic features and management of 43 cases of pneumonitis from two separate institutions, Memorial Sloan Cancer Center and the Melanoma Institute of Australia. Patients received anti-PD-1/PDL1 monotherapy or a combined regimen with anti-cytotoxic T cell lymphocyte-4 mAb. Any grade pneumonitis developed in approximately 5% of patients treated with anti–PD-1/PD-L1 mAbs, and grade 3 and higher pneumonitis developed in 1%. Pneumonitis was more common in patients treated with anti–PD-1/PD-L1 mAbs plus anti–CTLA-4 mAb compared with anti–PD-1/PD-L1 monotherapy. [24]

Clinically, nearly all cases of pneumonitis improved/resolved with drug holding and/or immunosuppression. However, some cases worsened and were fatal. In this series, worsening cases were restricted to current and former smokers and were more common in patients with underlying lung conditions; such patients may require particularly careful management. Among patients in whom pneumonitis improved/resolved, 12 (all with grade 1 to 2) underwent rechallenge with anti–PD-1/PD-L1 mAbs, and recurrent pneumonitis occurred in three (25%).

This may suggest that in mild cases, one may cautiously resume therapy after pneumonitis has improved/resolved and after careful discussion with the patient. Although most instances of pneumonitis were not severe, five deaths occurred, and in three cases, infection from prolonged immunosuppression contributed to death. No patient who received immunosuppression beyond corticosteroids (infliximab with or without cyclophosphamide) recovered from pneumonitis.

Improvement is needed in the choice, dose, and duration of therapies for pneumonitis with consideration of the role of antimicrobial prophylaxis.

Renal events: acute interstitial nephritis. Immune-induced nephritis is uncommon (related all-grade events

on CheckMate025 3.2%, per FDA label), but likely occurs fairly early in most patients (median time 10.6 weeks).[2] As an acute tubulo-interstitial nephritis, it typically manifests with urinalysis demonstrating WBC, RBC, and WBC casts.[25] Renal biopsy is rarely considered in RCC patients, the majority of which have solitary kidneys. In the event of severe acute kidney injury (AKI) checkpoint inhibitor therapy should immediately be discontinued, and corticosteroid therapy should be initiated promptly (e.g. 1mg/kg per day during 1 month followed by rapid tapering). The choice of withdrawing or reintroducing ICI should be decided upon after multidisciplinary discussion that includes defining the cancer status and its prognosis, the risk of end-stage renal disease account.

Conclusion

The advent of immune checkpoint inhibition in the treatment of RCC has helped to usher in a new era in managing this disease. With that, oncologists are facing a new spectrum of class specific toxicities, immune mediated adverse events Additional checkpoint inhibitors and numerous combination regimens are under investigation. Early data suggests that particularly the combination of two such immunomodulators may increase the incidence of immune related toxicities,[26] highlighting the relevance of understanding and better managing these phenomena. As the clinical experience with immune checkpoint inhibitors grows, it is imperative to rapidly identify side effects and promptly initiate adequate management to improve outcomes while not detracting from the efficacy of checkpoint inhibition. Prospective data are still needed to further elucidate optimal strategies for specific immunosuppressive treatment; however, by adhering to established guidelines for such therapy, clinicians are more likely to realize the potential benefits of checkpoint blockade.

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Cardiovascular Events and Torsades de Pointes in Patients Using Pazopanib and Other Marketed Anti-VEGF Agents for Metastatic Renal Cell Carcinoma: A Descriptive Study

Sumitra Shantakumar[1], Samantha St. Laurent[2], Myrthe van Herk-Sukel[3], Jeanenne J. Nelson[4]

Affiliations: [1]GlaxoSmithKline, Worldwide Epidemiology, Research Triangle Park, NC, USA; [2]GlaxoSmithKline, Worldwide Epidemiology, Waltham, MA, USA; [3]PHARMO Institute for Outcomes Research, Utrecht, Netherlands; [4]GlaxoSmithKline, Collegeville Road, Collegeville, Pennsylvania, 19426-0989, United States

Summary

Pazopanib is an angiogenesis inhibitor approved by the FDA in 2009 for metastatic renal cell carcinoma (RCC). This observational study describes the frequency of cardiovascular outcomes in adult RCC patients treated with pazopanib. A retrospective cohort study was conducted using data from the United States (Clinformatics™ DataMart Multiplan, IMPACT) and The Netherlands (PHARMO Database Network). The following outcomes were captured via ICD-9 diagnostic codes: myocardial infarction (MI), unstable angina (UA), Torsades de Pointes (TP), cerebrovascular accident (CVA), and transient ischemic attack (TIA). Incidence proportions were evaluated in pazopanib users and a comparator group of RCC patients treated with bevacizumab, sorafenib, or sunitinib. When multiple events occurred for the same cardiovascular outcome in the same patient, only the first event was used. Among 104 RCC patients treated with only pazopanib in the US population, 13 events occurred among 10 patients, as follows: five CVA [4.8% (95% CI: 1.6-10.9%)], three events each of MI and TIA [2.9%, (95% CI: 0.6-8.20%], and one event each of TP and UA [1.0% (95% CI: 0.02-5.2%)]. In comparison, the frequency of events among the comparator group (n=556) were: CVA (2.2%), MI (4.5%), TIA (1.4%), TP (1.6%), UA (1.6%). In the Dutch population, 21 pazopanib users and 96 patients in the comparator group met the eligibility criteria; one pazopanib patient experienced a CVA event and one sunitinib user had an UA event. The frequency of selected cardiovascular events among RCC patients was similar for users of pazopanib and similar drugs.

Clinical Practice Points

As part of pharmacovigilance activities, we evaluated 'real world' rates of cardiovascular events in RCC patients treated with pazopanib and other marketed anti-VEGF agents.

Based on data from a large administrative claims database in the United States and hospital records in The Netherlands, cardiovascular ischemic events occurred in 0-9.5% of RCC patients treated with pazopanib and other anti-VEGF agents over a mean of 379 days of follow-up.

Introduction

Pazopanib is an angiogenesis inhibitor approved in 2009 by the United States Food and Drug Administration (FDA) for treatment of metastatic renal cell carcinoma (RCC). The safety profiles of other marketed anti-vascular endothelial growth factor (anti-VEGF) drugs at the time of initial pazopanib approval suggested an increased occurrence of cardiovascular ischemic events and Torsades de pointes (TP).[1-6] As pazopanib is used to treat highly vascularized tumors, we designed a descriptive study as part of pharmacovigilance and post-marketing drug safety evaluations in the post-approval period to evaluate the occurrence of cardiac events and TP in RCC patients treated with pazopanib.

The primary objective of this study was to estimate the frequency of specific cardiovascular events and TP after drug initiation in adult (18+ years) pazopanib users with RCC and in a comparator group of RCC patients using three other marketed anti-VEGF agents at the time of pazopanib FDA approval in 2009: bevacizumab, sorafenib,

Keywords: cardiovascular, ischemia, pazopanib, renal cell carcinoma, Torsades de Pointes

Corresponding Author: Sumitra Shantakumar, PhD; Worldwide Epidemiology, Glaxosmithkline R&D; 150 Beach Road, Gateway West, #26-00; Singapore 189720, SINGAPORE Tel: +065-6232-8258; E-mail: sumitra.y.shantakumar@gsk.com

and sunitinib. A comparator group allowed for descriptive evaluation of three other drugs in the anti-VEGF class in order to place the pazopanib-specific results in context.

Patients and Methods

A descriptive, retrospective cohort study was conducted using two de-identified data sources: a US healthcare claims database, the Clinformatics™ DataMart Multiplan (IMPACT), a product of OptumInsight Life Sciences Inc., and the PHARMO Database Network in The Netherlands. The IMPACT system is a comprehensive, de-identified inpatient and outpatient health insurance claims database with more than 107 million non-elderly, insurance-carrying patients participating in 46 different healthcare plans, serving members across nine census regions in the US. The PHARMO Database Network is a population-based medical record tracking system covering 65 municipal areas with 3.2 million community-dwelling inhabitants of the Netherlands. The two specific PHARMO databases linked for this study were the Dutch National Medical Register that reflects all hospital admissions, and the outpatient pharmacy database containing drug dispensing information from community pharmacies.

Inclusion criteria for the anti-VEGF cohorts were tailored to each data source due to differences in database structure. For IMPACT, RCC patients were included if prescribed or administered pazopanib or one of the other specified anti-VEGF agents on or after October 1, 2009, the FDA approval date for pazopanib in the US Drugs were identified by text string and/or National Drug Codes. A one year screening window from October 1, 2008 until September 30, 2009 was used to identify any anti-VEGF drugs used prior to the study start date. The study index date was the first administration or prescription for the only or first anti-VEGF agent after October 1, 2009. Identified using an ICD-9 diagnostic code (189.0), the RCC diagnosis had to occur October 1, 2008 or later and must have occurred no later than 30 days after the anti-VEGF index date.

Patients using only one anti-VEGF drug during the study period were examined separately from those with more than one drug, as were patients using an anti-VEGF drug in a first-line (1L) setting versus a subsequent line of treatment. A first-line therapy was defined as drug treatment received before another anti-VEGF drug. Second-line or higher therapies are those received following another anti-VEGF drug. For patients with multiple anti-VEGF use, outcomes are listed by the therapy that was taken closest prior to or at the time of the cardiovascular event.

Patients were followed from the index date to the earliest event for each cardiovascular outcome, death, or until the end of study follow-up, September 30, 2012, whichever was reached first. Patients with another primary cancer diagnosis in the five years prior to the index date were excluded and continuous IMPACT enrolment with pharmacy benefits since October 1, 2009 was required for study inclusion. Patients with a history of cardiovascular events prior to the index date were not omitted.

For the PHARMO Database Network, RCC patients were included if an anti-VEGF had been dispensed or administered on or after February 1, 2011 (date of first pazopanib prescription in The Netherlands). The first dispensing or administration within this period was defined as the index date; drugs were identified by ATC codes (pazopanib, L01XE11; sorafenib, L01XE05; sunitinib, L01XE04). Hospitalization for RCC was used as a proxy for RCC diagnosis, based on primary or secondary hospital discharge diagnoses codes occurring at any time before or after the index date. Patients were excluded if diagnosed with a secondary cancer between the RCC hospitalization and the index date or if less than one year of medical history data prior to the index date was available. RCC was not an approved indication for bevacizumab in the Netherlands at the time of pazopanib approval, and hence was not assessed with the PHARMO data. Primary hospitalization codes were used to capture the cardiovascular outcomes; secondary codes were not included as they may relate to prevalent disease. Patients were followed until the date of cardiovascular event, death, end of the study period (December 31, 2012), or end of follow-up in the database (either by moving outside the PHARMO catchment area or end of data collection in the pharmacy), whichever occurred first.

The following cardiovascular outcomes were captured via ICD-9 diagnostic codes, as follows: myocardial infarction (MI), 410.9; unstable angina (UA), 411.1; Torsades de Pointes (TP), 426.82; cerebrovascular accident (CVA), 434.91; and transient ischemic attack (TIA), 435.9. Separate incidence proportions (cumulative incidence) and corresponding 95% confidence intervals (CI) were calculated for each type of cardiovascular event in the pazopanib and comparator groups. Each CI was calculated using the exact binomial method. When multiple events for a patient occurred for the same cardiovascular outcome, only the first event was used for the incidence analyses.

Results

The study population was 71% male and the median age was 61 years. Among pazopanib users, 40% (4/10) of patients who experienced an outcome during the study period had a history of cardiovascular events in the year prior to index date (**Table 1**).

No bevacizumab-only patient with cardiovascular events occurring during the study period experienced cardiovascular events in the prior year. However, 38% (5/13) of sorafenib-only and 14% (4/29) of sunitinib-only patients with cardiovascular events during the study period also had a cardiovascular event in the year prior to the index date.

In IMPACT, a total of 226 pazopanib users and 610 patients treated with the other anti-VEGF agents met the eligibility criteria. The mean and median follow-up time was 413 and 347 days, respectively, for pazopanib pa-

tients and 366 and 268 days, respectively, for patients treated with the other agents. Among 104 RCC patients treated solely with pazopanib following the index date (**Table 2**), 13 total events occurred among 10 patients as follows: five CVA events [4.8% (95% CI: 1.6-10.9%)], three events each of MI and TIA [2.9%, (95% CI: 0.6-8.20%], and one event each of TP and UA [1.0% (95% CI: 0.02-5.2%)]. The median time to event among pazopanib-only patients was shortest for the five CVA events (29 days) and longest for patients experiencing a TP event (580 days).

In comparison, the incidence proportions for cardiovascular events among the comparator group with users of one other anti-VEGF drug (n=556) were: CVA [2.2% (95% CI: 1.1-3.7%)], MI [4.5% (95% CI: 2.9-6.6%)], TIA [1.4% (95% CI: 0.6-2.8%)], TP [1.6% (95% CI: 0.7-3.1%)], UA [1.6% (95% CI: 0.7-3.1%)]. Among the comparator group using only one drug, the shortest median time to event was observed among patients experiencing a TIA event (96 days); the longest median time to event was found for UA events (337 days). The majority (69%) of the comparator group was comprised of sunitinib-only users and most cardiovascular events (38/63, 60%) were observed among patients treated with sunitinib only. However, the highest incidence proportion observed among non-pazopanib users with only one line of therapy was found for MI events in patients treated only with sorafenib [8/84, 9.5% (95% CI: 4.2-17.9%)].

Table 1. Characteristics of RCC patients treated with single agent or multiple anti-VEGF therapy, stratified by cardiovascular event after study index date (IMPACT database).

	CV Event after Study Index	N (%)	CV Event in Year Prior to Index (%)	Male (%)	Median Age, years
Pazopanib Only	No	94 (90%)	13%	74%	61
(n=104)	Yes	10 (10%)	40%	50%	64
Bevacizumab Only	No	79 (92%)	15%	66%	65
(n=86)	Yes	7 (8%)	0	71%	63
Sorafenib Only	No	71 (85%)	10%	80%	61
(n=84)	Yes	13 (15%)	38%	92%	65
Sunitinib Only	No	357 (92%)	6%	71%	59
(n=386)	Yes	29 (8%)	14%	79%	62
Multiple: Pazopanib first	No	20 (91%)	10%	65%	58
(n=22)	Yes	2 (9%)	0	100%	63
Multiple: Pazopanib not first	No	79 (79%)	8%	68%	60
(n=100)	Yes	21 (21%)	24%	71%	58
Multiple: no Pazopanib	No	50 (93%)	8%	60%	61
(n=54)	Yes	4 (7%)	50%	50%	78

Abbreviations: cardiovascular (CV), renal cell carcinoma (RCC), vascular endothelial growth factor (VEGF).

The incidence proportions for cardiovascular events occurring in RCC patients treated with multiple anti-VEGF therapies are shown in **Table 3**.

Events are listed by the anti-VEGF therapy that was taken closest prior to or at the time of the cardiovascular event; the denominator is comprised of all subjects who received each therapy either prior to another therapy (first line) or following another therapy (second line or higher). Among first line pazopanib patients (n=22), no events occurred. Nine events were observed among patients treated with pazopanib in the second line or higher setting (n=100), 5 CVA events [5% (95% CI: 1.6-11.3%)] and one event each for MI, TIA, TP and UA [1% (95% CI: 0.03-5.5%)]. Results for the other anti-VEGF agents used in the first or second line setting were similar.

In the PHARMO Database Network, a total of 21 pazopanib users, 6 sorafenib users, and 90 sunitinib users met the eligibility criteria. One pazopanib patient had a CVA event and one sunitinib user experienced a UA event; no other outcomes were observed during the study period [data not shown]. These patient and event numbers were too low to perform incidence analyses.

Discussion

The analyses from this descriptive study indicate that the cardiovascular events under investigation occurred in 0-9.5% of RCC patients treated with pazopanib or other anti-VEGF agents. To our knowledge, population-based estimates for these outcomes in pazopanib users do not exist. Cardiac or cerebral ischemic events were rare, but occurred in clinical trials of pazopanib among patients with advanced RCC.[7-9] In the pivotal phase III trial, arterial thrombotic events consisting of MI, CVA or TIA occurred in 3% of patients receiving pazopanib compared to none in the placebo arm.[10] A recent meta-analysis of arterial thrombotic events in patients from 19 randomized controlled trials of cancer patients treated with anti-VEGF drugs, including pazopanib, reported an overall incidence proportion of 1.5%; cardiac infarction/ischemia was the most common event type.[11]

Considering the low survival rates associated with advanced metastatic RCC, it is possible that mortality is a competing risk with non-fatal events observed only among survivors. This study is primarily focused on pa-

Table 2. Incidence proportions and time to event for cardiovascular events occurring in RCC patients treated with only one anti-VEGF therapy in the IMPACT database.

Anti-VEGF Therapy	Event	*n* Events/ *N* Total	Incidence Proportion (95% CI)	Median Time to Event (days)
Pazopanib Only	CVA	5/104	4.8% (1.6-10.9)	29
	MI	3/104	2.9% (0.6-8.2)	153
	TIA	3/104	2.9% (0.6-8.2)	271
	TP	1/104	1% (0.02-5.2)	692
	UA	1/104	1% (0.02-5.2)	580
Bevacizumab, Sorafenib or Sunitinib Only	CVA	12/556	2.2% (1.1-3.7)	122
	MI	25/556	4.5% (2.9-6.6)	131
	TIA	8/556	1.4% (0.6-2.8)	96
	TP	9/556	1.6% (0.7-3.1)	237
	UA	9/556	1.6% (0.7-3.1)	337
Bevacizumab Only	CVA	1/86	1.2% (0.03-6.3)	631
	MI	3/86	3.5% (0.7-9.9)	338
	TIA	3/86	3.5% (0.7-9.9)	161
	TP	0/86	n/a	n/a
	UA	2/86	2.3% (0.3-8.2)	324
Sorafenib Only	CVA	4/84	4.8% (1.3-11.8)	96
	MI	8/84	9.5% (4.2-17.9)	37
	TIA	0/84	n/a	n/a
	TP	3/84	3.6% (0.7-10.1)	561
	UA	1/84	1.2% (0.03-6.5)	442
Sunitinib Only	CVA	7/386	1.8% (0.7-3.7)	192
	MI	14/386	3.6% (2.0-6.0)	209
	TIA	5/386	1.3% (0.4-3.0)	19
	TP	6/386	1.6% (0.6-3.4)	164
	UA	6/386	1.6% (0.6-3.4)	363

Abbreviations: cerebrovascular accident (CVA), confidence interval (CI), myocardial infarction (MI), renal cell carcinoma (RCC), Torsades de Pointes (TP), transient ischemic attack (TIA), unstable angina (UA), vascular endothelial growth factor (VEGF)

zopanib users; data for the three other drug groups are included to provide a general pattern and context for the pazopanib results. This study was not designed to estimate head-to-head comparisons of event rates between drugs. Thus, no formal drug-to-drug statistical analyses were conducted.

This study was limited by the small number of subjects in several analytic groups, including the line of therapy analyses, resulting in some imprecise estimates. The estimates of effect presented are proportions; thus, assessments accounting for differing time on the prescribed agents cannot be made. Further, the IMPACT claims database lacks key cardiovascular risk factor information such as smoking, alcohol use, obesity, ethnicity, or family history. The elderly population are under-represented in the U.S. data as their healthcare is covered by Medicare. In PHARMO, out-patient pharmacy data were used to define drug exposure. As a consequence, patients starting oral anti-VEGFs during their hospital stay would not have inpatient initiation captured, thus truncating duration for the anti-VEGF drug. Further, the use of hospitalization data to identify cardiovascular outcomes may have missed events treated in an outpatient setting (such as TIA) or patients who died prior to hospitalization.

A strength of this observational study is the focus on patients from two real-world population-based settings, representing drug use in the broader general population compared to clinical trial patients, where a large number of inclusion and exclusion criteria create a more select population. Cardiovascular and cerebrovascular outcomes are well captured via ICD-9 diagnosis codes in administrative data.[12,13] The IMPACT database includes a large number of patients and covers a wide variety of geographic areas.

Conclusions

In conclusion, the frequency of selected cardiovascular events among population-based RCC patients was similar for users of pazopanib and other anti-VEGF drugs in this study. Results from clinical trials suggest that anti-VEGF treatments may be associated with an increased risk of developing cardiovascular events among cancer patients.[11] More observational epidemiologic studies of are needed to better understand this relationship in the general cancer population.

Acknowledgement

Page Abrahamson provided manuscript writing and editing support. This study was sponsored by GlaxoSmithKline; pazopanib is an asset of Novartis AG as of March 1, 2015. GlaxoSmithKline provided financial support for the conduct of the research and preparation of the article, including the collection, analysis and interpretation of data and writing of the report.

Conflict of Interest

SS, SSL, and JJN are current employees of GlaxoSmithKline; they also hold GSK shares. MvHS is an employee of the PHARMO Institute. This independent research institute performs financially supported studies for government and related healthcare authorities and several pharmaceutical companies.

Author Contributions

SS and JJN were responsible for the study design and drafting of the manuscript. SSL and MvHS were responsible for data acquisition and statistical analysis. All authors were involved with data interpretation and critical revision of the manuscript content.

Funding

This study was sponsored by GlaxoSmithKline; pazopanib is an asset of Novartis AG as of March 1, 2015.

Role of the Funding Source

GlaxoSmithKline provided financial support for the conduct of the research and preparation of the article, including the collection, analysis and interpretation of data and writing of the report.

Ethical Approvals and Informed Consent

IMPACT data were anonymized and compliant with U.S. Health Insurance Portability and Accountability Act (HIPAA) guidelines; ethical board review was obtained at PHARMO.

Table 3. Incidence proportions for cardiovascular events occurring in RCC Patients treated with multiple anti-VEGF therapies in the IMPACT Database

Anti-VEGFLine of Therapy	Cardiovascular Event	n Events/ N Total	Incidence Proportion (95% CI)
First Line Therapy*			
1L Pazopanib	CVA, MI, TIA, TP, UA	0/22	n/a
1L Bevacizumab	CVA	1/12	8.3% (0.2-38.5)
	MI, TIA, TP, UA	0/12	n/a
1L Sorafenib	CVA	1/33	3.0% (0.1-15.8)
	TP	1/33	3.0% (0.1-15.8)
	MI, TIA, UA	0/33	n/a
1L Sunitinib	CVA	5/109	4.6% (1.5-10.4)
	MI	5/109	4.6% (1.5-10.4)
	TIA	4/109	3.7% (1.0-9.1)
	TP	0/109	n/a
	UA	3/109	2.8% (0.6-7.8)
Second Line Therapy or Higher**			
2L+ Pazopanib	CVA	5/100	5.0% (1.6-11.3)
	MI	1/100	1.0% (0.03-5.5)
	TIA	1/100	1.0% (0.03-5.5)
	TP	1/100	1.0% (0.03-5.5)
	UA	1/100	1.0% (0.03-5.5)
2L+ Bevacizumab	MI	2/38	5.3% (0.6-17.8)
	CVA, TIA, TP, UA	0/38	n/a
2L+ Sorafenib	CVA	1/46	2.2% (0.1-11.5)
	MI	1/46	2.2% (0.1-11.5)
	TIA	0/46	n/a
	TP	0/46	n/a
	UA	1/46	2.2% (0.1-11.5)
2L+ Sunitinib	CVA, MI, TIA, TP, UA	0/21	n/a

Abbreviations: cerebrovascular accident (CVA), confidence interval (CI), myocardial infarction (MI), renal cell carcinoma (RCC), Torsades de Pointes (TP), transient ischemic attack (TIA), unstable angina (UA), vascular endothelial growth factor (VEGF).
*First-Line (IL): Therapy received before another anti-VEGF drug. **Second-Line or Higher (2L+): Therapy received following other anti-VEGF drug(s). The listed therapy was the closest therapy received prior to or

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Sunitinib and Zoledronic Acid Combination Therapy for Metastatic Renal Cell Carcinoma: Alarming for Osteonecrosis of the Jaw

Alexander M. Won, DDS
Assistant Professor
Department of Head and Neck Surgery, Unit 1445
The University of Texas MD Anderson Cancer Center
Houston, Texas

Theresa M. Hofstede, DDS
Associate Professor
Department of Head and Neck Surgery, Unit 1445
The University of Texas MD Anderson Cancer Center
Houston, Texas

Richard Cardoso, DDS, MS
Assistant Professor
Department of Head and Neck Surgery, Unit 1445
The University of Texas MD Anderson Cancer Center
Houston, Texas

Adegbenga O. Otun, BDS
Assistant Professor
Department of Head and Neck Surgery, Unit 1445
The University of Texas MD Anderson Cancer Center
Houston, Texas

Mark Chambers, DMD, MS
Professor
Department of Head and Neck Surgery, Unit 1445
The University of Texas MD Anderson Cancer Center
Houston, Texas

Introduction

As medical treatment of serious diseases such as cancer lengthens patient survival, the side effects of new drugs are beginning to present in community dentists' patients. The most well-known example is probably bisphosphonate-related osteonecrosis of the jaw (ONJ), which was first reported in 36 patients in 2003 by Marx[1]; all 36 patients had been treated with zoledronic acid, an antiresorptive bisphosphonate typically used to treat osteopenia or osteoporosis or bone destruction due to cancer. In 2004, Ruggiero et al[2] reported another 63 patients with osteonecrosis caused by zoledronic acid. Based on that evidence, in 2005, the United States Food and Drug Administration issued a warning for the entire bisphosphonate drug class for possible ONJ. More recently, with advancements in cancer treatment utilizing therapies such as RANK ligand inhibitors and angiogenesis inhibitors, the risk of ONJ appears to have been increased further still.

Angiogenesis inhibitors short-circuit cancer growth by inhibiting blood vessel formation in tumors. One way cancer cells grow is by releasing a protein called vascular endothelial growth factor (VEGF) to signal the need for blood vessel growth; sunitinib, a tyrosine kinase inhibitor (TKI) and antiangiogenic agent, binds to receptors on epithelial or endothelial cells to block VEGF activity. After several case reports described the occurrence of osteonecrosis in cancer patients who received targeted therapies, specifically TKIs and monoclonal antibodies targeting VEGF, the American Association of Oral and Maxillofacial Surgeons in 2014 expanded the concept of bisphosphonate-related ONJ to what is now termed medication-related ONJ.[3]

Targeted therapies play an integral role in cancer care and can cause many types of oral complications. Therefore, patients should be aware of the potential complications caused by angiogenesis inhibitors in addition to bisphosphonates.

Here we present a case in which a patient receiving sunitinib with a history of zoledronic acid therapy developed extensive ONJ.

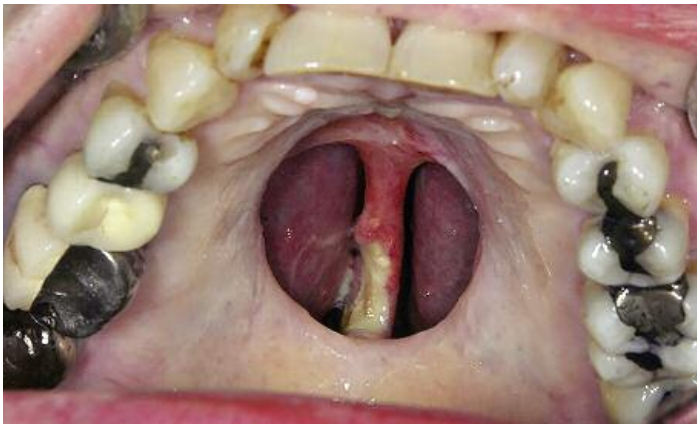

Figure 1.

Keywords: Osteonecrosis, medication related osteonecrosis, jaw disease, bone necrosis

Corresponding Author: Alexander M. Won, DDS, Assistant Professor, Department of Head and Neck Surgery, Unit 1445, The University of Texas MD Anderson Cancer Center, 1400 Pressler Street, Houston, Texas 77030; Phone: 713-745-8353; Fax: 713-794-4662
E-mail: amwon@mdanderson.org

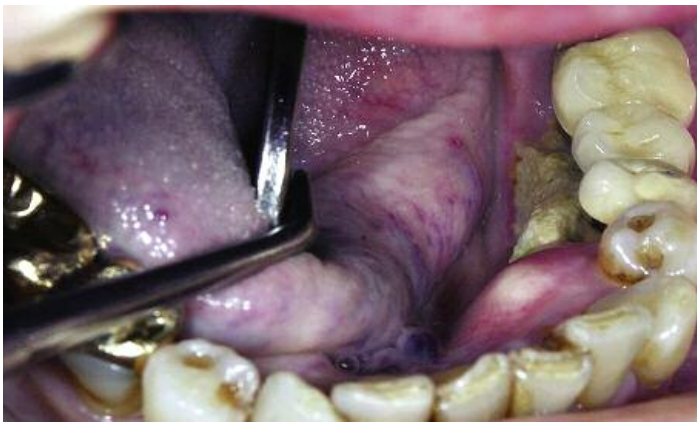

Figure 2.

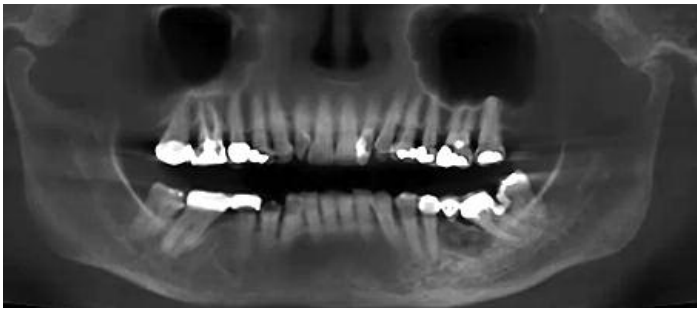

Figure 3.

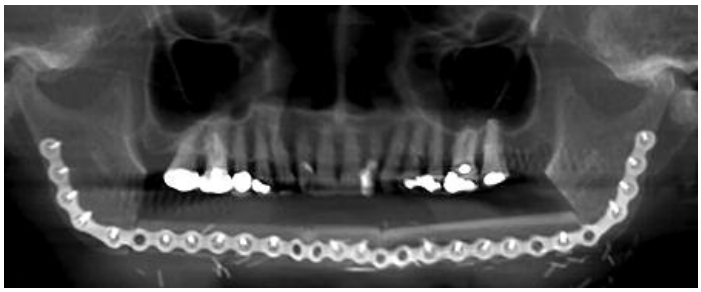

Figure 4.

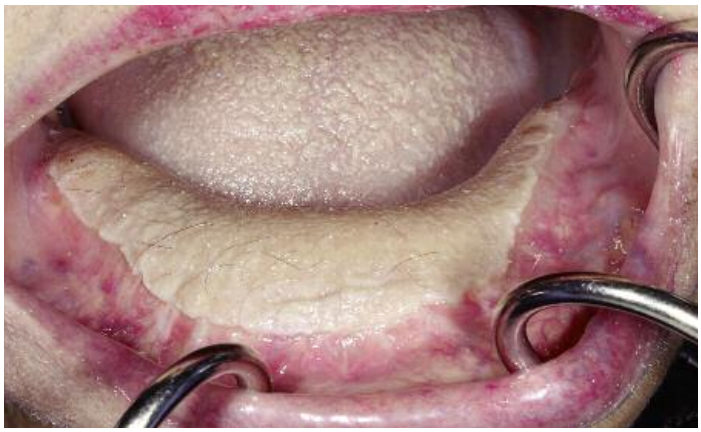

Figure 5.

Case Descriptions

A 73-year-old woman presented to The University of Texas MD Anderson Cancer Center oral oncology clinic for evaluation of a large hard palate defect communicating into the nasal cavity and exposed bone on the left mandible. The patient had been diagnosed with metastatic renal cell carcinoma (RCC) and had been treated with sunitinib for the previous 2 years. The patient received sunitinib (37.5 mg) on a daily basis for 4 weeks before surgery to remove the RCC and did not receive sunitinib for 2 weeks after the surgery. After this 2-week period, the patient was treated with a maintenance dose of sunitinib (37.5 mg, 3 days a week). The patient also had zoledronic acid (4mg) IV infusions every 4 weeks for 3 months (Total of 3 infusions) owing to a left iliac osteolytic bone lesion.

Six months before presenting at our clinic, the patient saw her local dentist for a routine check-up. She developed a small laceration on her hard palate caused by the edge of the film used when the dentist performed routine radiography. The laceration progressed to a large nonhealing wound. The bony hard palate became involved with deterioration, leading to sequestration of bone and tissue from the mouth. Intraoral examination revealed a large, 3-cm defect on the midline of the hard palate, communicating into the nasal cavity but not extending into the soft palate (**Fig 1**). The left posterior lingual mandibular area had 1.5 cm bone exposure under the 3-unit fixed dental prosthesis #18-20 (Figs **2**,**3**). An obturator prosthesis was fabricated to close the oral-nasal communication. The exposed left lingual mandibular necrotic bone eventually progressed to the midline and extended inferiorly to the floor of mouth. A new site of exposed bone was identified on the right mandible measuring 1cm. Due to inability to control progression necrosis and pain of the jaw, the patient underwent a subtotal mandibulectomy and immediate fibula free flap reconstruction and placement of a reinforcing and stabilizing titanium reconstruction plate (Synthes TruMatch Proplan). (**Fig 4**, **5**) Following 6 months healing phase, removable mandibular resection prosthesis was fabricated. (**Fig 6**) This prosthesis will help with oral functional difficulties including poor lip support, drooling of saliva, poor bolus control and speech disturbance. The patient requires a mandibular resection prosthesis, which will help maintain functional positioning of the jaws, improve speech, mastication and deglutition.

Discussion

The case report describes a patient who developed extensive stage III medication-related ONJ on the hard palate and mandible, in which she underwent subtotal mandibulectomy with immediate fibula free flap reconstruction. Patients with advanced RCC with bone metastases are typically treated with a combination of TKIs, such as sunitinib, and zoledronic acid. This combination improves median overall survival and has better treatment efficacy than other regimens.[4] However, several studies showed that the combination of sunitinib and zoledronic acid increases the incidence of ONJ in patients with metastatic renal cell carcinoma.[4-7] Fusco et al[7] conducted a multicenter study of metastatic renal cell cancer treated with bisphosphonates and targeted agents. They concluded that ONJ is not a rare occurrence and attributed its icrease

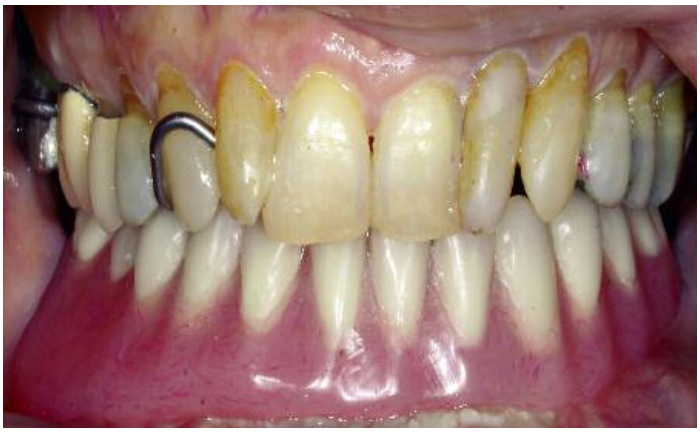

Figure 6a.

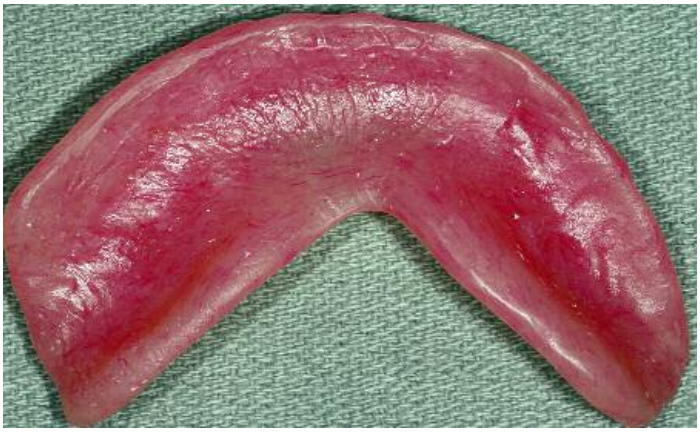

Figure 6b.

to the increase in life expectancy due to use of new targeted cancer drugs, such as sunitinib, and therefore longer exposure to bisphosphonate treatments. The median duration of bisphosphonate administration was 12 months before developing medication-related ONJ. However, the 3 doses of zoledronic acid may have had some kind of an exacerbating effect.

Osteonecrosis can also occur with targeted therapy alone. Multiple case reports have reported the development of ONJ in patients who received targeted antiangiogenic therapies but who were bisphosphonate naïve.[8-10]

Although it has been more than a decade since the first case of bisphosphonate-related ONJ was reported, the pathophysiology of the disease is not fully understood. Santini D et al showed cancer patients treated with zoledronic acid had dramatic decreased circulating VEGF levels.[11] Because VEGF is important in normal jawbone remodeling and wound repair, researchers have suggested that inhibition of VEGF activity could potentially lead to ONJ.[9]

Targeted therapies, such as TKIs, play integral roles in cancer care but result in a variety of oral complications and some long-term side effects of these drugs are still unknown. Although the risk of developing ONJ from TKIs or zoledronic acid are extremely rare, combination of the two may have a synergetic affect. As patients receiving such treatments are living longer and are returning to their community caregivers after their cancers have been cured or rendered stable, patients should be aware of the potential for serious complications and take appropriate precautions in their care.

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EDITOR'S MEMO

(continued from page 34)

CABOSUN trial is viewed at a regulatory level and how these other IO combinations come forward.

Take-home on treating kidney cancer. The key to kidney cancer treatment is to tailor a patient's therapy and the schedule. In patients who can receive full doses, you want to be sensitive to their co-morbidities, because comorbidities limit our ability to give full doses. You want to make sure you address the toxicities associated with targeted therapy—persistently and throughout their course. I tell my patients when I first see them that the beginning of the treatment will be a bit more difficult until we get a handle on toxicity specific to them. Over time, we manage it quite well—we change schedule, we try not to modify dose, we pick patients appropriately and try to match the patient, regimen and the opportunity for best outcome.

Robert A.Figlin, MD
Editor-in-Chief

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sequencing and timing were assessed.

The study identified 133 patients, of whom 28 received a CTLA-4 inhibitor alone, 88 received a PD-1 inhibitor alone, and 17 received both classes of inhibitors either sequentially (n=13) or concurrently (n=4). Fifty-six patients received radiation within 14 days of an immune checkpoint inhibitor. Forty-six patients experienced at least 1 ir-AE (34.6%). Patients receiving both CTLA-4 and PD-1 inhibitors experienced more any-grade ir-AEs as compared with either individually (71% vs 29%, *P*=.0008). Any-grade ir-AEs occurred in 39% of patients in whom radiation was administered within 14 days of immunotherapy, compared with 23% of other patients (*P*=.06) and more often in patients who received higher equivalent dose in 2-Gy fractions (EQD2) EQD2 (*P*=.01). However, most toxicities were mild. There were no associations between site irradiated and specific ir-AEs.

Conclusion: The data suggest the combination of focal palliative radiation and CTLA-4 and/or PD-1 inhibitors is well tolerated, with manageable ir-AEs that did not seem to be associated with the particular site irradiated. Although conclusions are limited by the heterogeneity of patients and treatments, and future confirmatory studies are needed, this information can help guide clinical practice for patients receiving immune checkpoint therapy who require palliative radiation therapy.

Correlation of genomic alterations assessed by next-generation sequencing (NGS) of tumor tissue DNA and circulating tumor DNA (ctDNA) in metastatic renal cell carcinoma (mRCC): potential clinical implications. Hahn AW, Gill DM, Maughan B, et al. *Oncotarget*. 2017 May 16;8(20):33614-33620.

Summary: Tumor tissue and circulating tumor DNA (ctDNA) next-generation sequencing (NGS) testing are frequently performed to detect genomic alterations (GAs) to help guide treatment in metastatic renal cell carcinoma (mRCC), especially after progression on standard systemic therapy. This report assessed whether GAs detected by ctDNA NGS are different from those detected by tumor tissue NGS, specifically in patients with mRCC, and if these platforms are interchangeable or complimentary. When controlling for genes tested by both platforms, the median mutation rate for ctDNA was similar to tissue (median 3.0 vs. 1.0, p = 0.14). However, the concordance rate between the two platforms was only 8.6%. When the study compared GAs by molecular pathway, GAs in tumor tissue were more common for the DNA repair and epigenetic pathways. Results of NGS testing from tumor tissue and ctDNA from 19 sequential mRCC patients were compared. GAs in each were statistically evaluated using the Wilcoxon signed-rank test. The Fischer's exact test was used to compare the incidence of mutations in selected molecular pathways.

Conclusion: When controlling for genes tested by both platforms, similar number of GAs were detected by both tissue and ctDNA based NGS. However, there was discordance in the type of GAs detected suggesting that ctDNA NGS may be more reflective of dynamic tumor genomic heterogeneity. Hence, these two platforms may be considered complementary to each other, rather than interchangeable, for assessment of tumor GAs to guide selection of targeted clinical trial therapies.

Evolution of circulating tumor DNA profile from first-line to subsequent therapy in metastatic renal cell carcinoma. Pal SK, Sonpavde G, Agarwal N, et al. *Eur Urol*. 2017 Apr 13. pii: S0302-2838(17)30277-4.

Summary: Circulating tumor DNA (ctDNA) is a platform to noninvasively ascertain temporal changes in genomic profile. The ctDNA profile was obtained in mRCC patients who received ctDNA profiling as part of routine clinical care at progression using a 73-gene Clinical Laboratory Improvement Amendments-certified ctDNA platform. Genomic alterations (GAs) were pooled for the entire cohort. A comparison of first- and post first-line was performed with grouping based on conventional practice patterns (first-line regimens included sunitinib, pazopanib, and bevacizumab, and postfirst-line regimens included everolimus, axitinib, cabozantinib, and nivolumab). ctDNA clinical results from a nationwide cohort of 220 consecutive patients with mRCC were assessed (145 men, 75 women; median age: 63 yr, interquartile range: 57-70). GAs were detected in 78.6% of patients. The most frequent GAs in the overall cohort included TP53 (35%), VHL (23%), EGFR (17%), NF1 (16%), and ARID1A (12%). Thirty-eight and 64 patients were coded as receiving first-line and later line agents, respectively. The highest disparity in GA frequencies in postfirst-line versus first-line were in TP53 (49% vs 24%), VHL (29% vs 18%), NF1 (20% vs 3%), EGFR (15% vs 8%), and PIK3CA (17% vs 8%) while ARID1A was equivalent (13% vs 11%). Restricting the analysis to later lines versus first-line vascular endothelial growth factor inhibitors, these differences were even more prominent, particularly for TP53 (64% vs 31%) and NF1 (29% vs 4%).

Conclusion: In the largest assessment of ctDNA-detected GAs prevalence in mRCC to date, the majority of patients demonstrated clinically and biologically relevant GAs. Increasing p53 and mechanistic target of rapamycin pathway (eg, NF1, PIK3CA) alterations in post first-line patients with first-line vascular endothelial growth factor-directed therapy may underlie mechanisms of resistance. Routine ctDNA assessment during the clinical course of mRCC patients may have therapeutic implications. KCJ

Combination Therapies Dominate the Agenda of the Worldwide Meeting

Marc R. Matrana, MD, MS, FACP
Medical Director, Precision Cancer Therapies (Phase 1) Program, Ochsner Cancer Institute, New Orleans, Louisiana
Senior Lecturer, Ochsner Clinical School, University of Queensland, New Orleans, Louisiana and Brisbane, QLD, Australia.

Erin Pierce, MSN, APRN, FNP-C
Advanced Practitioner, Genitourinary Medical Oncology and Phase I Research, Ochsner Cancer Institute, New Orleans, Louisiana

Lorrie Erario, RN, OCN
Nurse Supervisor, Hematology and Medical Oncology Clinics, Ochsner Cancer Institute, New Orleans, Louisiana

The world of oncology once again convened in Chicago for our annual gathering aimed at conquering cancer and celebrating new developments, which are coming ever faster and more furious. Although once considered almost taboo in RCC, many of the most intriguing presentations and abstracts from the American Society of Clinical Oncology's (ASCO) annual meeting focused on various combination therapies in RCC, especially combinations invol- ving immunotherapies.

Highlights From Combination Studies

Epacadostat and pembrolizumab. The preliminary results of the phase I/II ECHO-202/KEYNOTE-037 study that paired epacadostat with pembrolizumab were quite promising. The phase I portion of the study did not identity a maximum tolerated dose as the combination was relatively well tolerated at all dose levels. The expansion cohort analyzed 19 patients who had received no prior treatment or one prior treatment; in this population, the overall response rate (ORR) and disease control rate (ORR + stable disease) were 47% and 58%, respectively. There were no responses in patients who had received two or more prior therapies, but a stable disease rate of 36% was achieved. 15% of patients experienced grade 3 or higher adverse events, and 2 subjected discontinued treatment due to toxicity.[1]

Avelumab and Axitinib. Another combination study that garnered a lot of attention at the meeting was a phase 1b trial that paired avelumab + axitinib for the first-line treatment of advanced RCC. 55 treatment-naïve patients with advanced RCC were treated with the combination. ORR was impressive at 54.5%, including 2 complete responses, toxicity was a concern, but seemed managable for most patients with 52 patients reporting axitinib-related adverse events (including frequent fatigue, diarrhea, hypertension, and dysphonia) and 51 of subjects reporting avelumab-related toxicities (including most frequently, diarrhea and fatigue). Four patients discontinued axitinib and five patients discontinued avelumab due to toxicities. The results certainly warrant further study of this combination.[2]

Cabozantinib and nivolumab. One of the most interesting combinations reported came from an small, early trial that evaluated the safety and clinical activity of the combination of cabozantinib and nivolumab as well as the triple combination of cabozantinib, nivolumab, and ipilumumab in patients with patients with a variety of genitourinary cancer patients, including two patients with conventional RCC and two patients with sarcomatoid dedifferentiation. Both combinations were surprisingly relatively well tolerated with no dose limiting toxicities noted. One of the patients with sarcomatoid dedifferentiation was noted to have a partial response, and responses were also seen in patients with other rare genitourinary malignancies including squamous cell carcinoma of the bladder, urachal, and penile cancers. Larger cohorts of testing the combination in bladder cancers and rare genitourinary tumors are ongoing.[3]

Atezolizumab and bevacizumab. The IMmotion150 study, another interesting phase II combination trial paired the checkpoint inhibitor atezolizumab with bevacizumab in the first-line setting in patients with previously untreated metastatic RCC and compared this to too other arms, one using only single agent atezolizumab and the other single agent sunitinib. Both comparator arms had the option of crossing over to the combination therapy at progression. In the 54% of PD-L1–positive patients, the median PFS was 14.7 months with the combination, 5.5 months with atezolizumab alone, and 7.8 months in sunitinib alone arm. 60% of patients receiving atezolizumab alone went on to receive the combination and demonstrated a 24% response rate, while 78% of patients

receiving sunitinib subsequently crossed over to the combination and achieved an overall response rates of 28%.

These outcomes suggest encouraging activity for the combination of atezolizumab + bevacizumab in both the first- and second-line setting for patients with metastatic RCC.[4]

Multikinase inhibitor and everolimus. CM082A small phase I study tested the combination of CM082, a novel oral multikinase inhibitor targeting VEGFR, PDGFR and CSF1R with a shorter half-life and limited tissue accumulation, designed to lower toxicity and enable combination with other therapies, everolimus in patients with metastatic renal cell carcinoma. At 200mg dose level, partial responses were noted in 5/14 (36%) patients, with a disease control rate of 71%. The median PFS was noted to be 5.7 months in this cohort. Toxicities were manageable, as well, warranting further investigation of this novel agent and combination.[5]

Pazopanib and pembrolizumab. Chowdhury et al reported the results of a small phase I/II study evaluating the combination of pazopanib and pembrolizumab. Overall, 35 patients were tested with combinations of pemborlizumab 2mg/kg and pazopanib at 600mg or 800mg; one cohort was treated with a sequential strategy of single-agent pazopanib followed by the combination. The study found that 80-90% of the patients in each cohort experienced grade 3 or 4 toxicities, especially hepatotoxicity, severely limiting the utility of this novel combination.[6]

Synergistic Effects With Radiation, Check Point Inhibitors

In addition to combinations of systemic therapies, preclinical data suggests that there are synergistic effects between radiation therapy and check point inhibitors. Lin and colleagues sought to explore the immunomodulatory activity of radiation therapy alone or in combination with pembrolizumab in solid tumors, including renal cell cancer. Twelve RCC patients who had progressed after first-line therapy received radiation therapy (8Gy x 1 or 4Gy x 5) followed by pembrolizumab or 1 dose pembrolizumab followed by radiation therapy then were given another dose of pemproliumab. Pre- and post- radiation tumor biopsies were obtained to evaluate PD-L1 expression and flow cytometry was performed before, during, and after treatment to assess immune markers. Grade 3 adverse effects experienced included fatigue, nausea, hyperglycemia, lymphopenia, thrombocytopenia and AST elevation (post RT for liver mets). Five patients had stable disease of 18 to 45 weeks and 4 patients had progression within 9 weeks. Preliminary flow cytometry findings showed consistently higher numbers of monocytes in non-responders compared to responders. CD4+, CD8+ and NK cells and other markers are also being analyzed. Overall, these results suggest that the combination of radiation therapy with pembrolizumab is tolerable while exhibiting clinical worth. Additionally, the adverse effect profile was not dramatically different when compared to single agent pembrolizumab.[7]

Encouraging Progress on Biomarkers

Finding clinically useful biomarkers in RCC has been a thorn in the side of researchers for decades now, still with no suitable candidates finding their way into standard daily practice. But a few studies presented do try to make some headway in this area. A study presented by Escuider sought to validate the 16-gene Recurrence Score in 212 patients with high-risk stage III disease from S-TRAC trial. Primary tissue from these patients was analyzed and it was found that time to recurrence and disease-free survival in patients receiving sunitinib or placebo were significantly predicted using the Recurrence Score. No significant interaction was reported between treatment and the Recurrence Score. The results further support the value of the Recurrence Score, which can be used to identify high-risk patients who may benefit from adjuvant treatment. Further studies to determine the predictive value of the score are necessary before it can be clinically used to select patients for adjuvant therapies. [8]

In the pursuit of reliable biomarkers in metastatic RCC patients, Arafat and colleagues reported on the development and clinical validation of predictive circulating tumor cell (CTC) biomarkers that will be assessed in the OMNIVORE trial. Findings show that CTC frequency and PDL1/HLA expression are lower in nivolumab responders versus patients with early progression. High but variable HLA expression suggests resistance mechanisms are variable. CTCs were found in 26 out of 27 patients using the RCC-specific CA IX antibody. Staining with CAXII and PAX8 confirmed CTC were of renal origin. The findings report the identification of clear cell RCC circulating tumor cells using CAIX, CAXII and PAX8 as confirmatory markers. The authors plan to further study the usefulness of these biomarkers in the phase II OMNIVORE trial, which examines ipilumimab efficacy in patients with stable or progressive disease on nivolumab alone.[9]

Adjuvant Therapy: New Results From PROTECT

Of course, an effective adjuvant therapy for RCC has been an elusive holy grail sought after almost as much as a reliable biomarker. Results of a randomized phase III trial of adjuvant pazopanib versus placebo after nephrectomy, called the PROTECT study, were presented. This large study included 1538 subjects with locally advanced RCC post-nephrectomy who were randomized to receive pazopanib vs placebo for 1 year following surgery. The dose of pazopanib had to be decreased from 800 mg to 600 mg to improve tolerability, and the primary endpoint of the study was changed to disease-free survival in 1135 patients. In the intent-to-treat population with the 800-mg dose a 31% reduced risk of recurrence was reported and in the much larger group of patients treated with 600mg a 20% reduction in risk of recurrence was noted; however, the primary endpoint was not met with pazopanib 600 mg. Treatment was discontinued frequently due to transaminitis.[10]

In the single arm phase II NeoSun trial, researchers sought to identify efficacy and safety of neoadjuvant and adjuvant sutinib in treatment naive metastatic RCC patients. 14 patients received neoadjuvant sunitinib at 50mg daily with 10 out of the 14 taking the total planned 12 doses. All 14 underwent total cytoreductive nephrectomy, and 13 received adjuvant sunitinib on a repeating 6 week cycle consisting of 4 week-on and 2 week-off, until disease progression. 58.3% of patients achieved confirmed response while 91.7% achieved clinical benefit. Median overall survival was 33.7 months and median progression free survival was 15.7 months. Among the patients who received partial or complete response, the median response time was 8.7 months. It is important to note that there were no unexpected surgical or sunitinib-related toxicities experienced showing sunitinib is safe when given in the neoadjuvant and adjuvant setting.[11]

Shepherd and colleagues provided an interesting look at how dynamic changes in clinical labs might help predict survival outcomes in patients receiving VEGF-targeted therapy for advanced clear cell RCC. Multiple models show that markers of systemic inflammatory response have prognostic value in ccRCC prior to starting treatment, but little is known about how dynamic changes in these markers occurring during therapy might be used to predict outcomes. These investigators conducted a retrospective analysis of data form a phase II study evaluating cediranib vs cediranib and saracatinib in patients with relapsed metastatic clear cell RCC. Specifically, they analyzed how haemoglobin, neutrophil count, platelet count, lactate dehydrogenase levels, and C-reactive protein were recorded at randomization, at 8-weeks into the study and at progression for 138 patients. Changes at each time point were compared. This analysis found that a rise in and C-reactive protein or neutrophil count at 8 weeks was predictive of poor outcome, while a fall in hemoglobin was predictive of poor outcomes and progressive disease. Certainly, additional investigation in this area is warranted.[12]

METEOR Offers Insights on Cabozantinib, Regardless of Nephrectomy

The debate regarding the usefulness of cytoreductive nephrectomy in the era of targeted therapies continues. Tannir, et al sought to provide more data to drive the discussion, by analyzing data from the phase 3 METEOR trial. This widely known trial compared cabozantinib to everolimus in 658 patients with advanced clear cell RCC who had previously received at least one VEGFR TKI. 85% of patients enrolled had a prior nephrectomy (7% partial). Tannir's analysis showed that baseline characteristics were less favorable for those 15% of subjects who had no prior nephrectomy. The analysis showed that cabozanitinib improved progression-free survival, overall survival, OS, and objective response rate when compared with everolimus regardless of nephrectomy status. The median overall survival was longer in the nephrectomy subgroup for both treatment arms (22.0 in those treated with cabozatinib who had a prior nephrectomy, 17.2 months in the everolimus prior nephrectomy group, 16.3 months in those treated with cabozantinib who had no nephretomy, and 12.5 months in patients treated with everolimus and no prior nephrectomy), but these outcomes may be more related to the differences in baseline characteristics than effects of nephrecotmy status.[13]

There is limited data about outcomes and predictors of patients with long-term response to targeted therapy, but Tannir and colleagues attempted to fill in some of this gap, but analyzing data from the COMPARZ study. They sought to identify patients from COMPARZ who exhibited a long-term response (10 months of greater) to pazopanib and sunitinib and to determine time to response while describing the clinical characteristics of patients who achieved such response. They found that among the 1,110 patients treated on the study, 14% had long-term responses to pazopanib and 13% had long-term responses to sunitinib. PFS was similar in both groups, however, in those treated with pazopanib, there was noted to be a shorter time to achieve a response (11.9 weeks [95% CI, 11.3–12.1] in the pazaopnib group compared to 17.4 weeks; [95% CI, 12.7–18.0]) in the sunitinib group, suggesting that this may be a more appropriate therapy for patients who require a more rapid response. [14]

While prospective clinical trial data is still the gold standard but which data in the field is judged, there is a more and more understanding as eligibility criteria for trials continues to tighten that outcomes data for real world populations (especially those not eligible for enrollment in prospective clinical trials) is sorely needed. Steven Yip and colleagues retrospectively reviewed real-world outcomes in metastatic RCC patients treated with immunotherapy using data from the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC). They identified 312 patients and found an ORR of 29% in all patients, which was consistent regardless of the line of therapy. They divided those patients treated with immunotherapy in the second-line setting into favorable, intermediate, and poor risk categories using the IMDC criteria and found that while the duration of treatment rate was not reached for those in the favorable risk category, patients in the intermediate risk category had a risk 8.6 months and those in the poor risk category remained on treatment only 1.9 months. Age did not appear to affect outcomes with the therapies.[15]

Drilling Down Into Data on Rare Kidney Cancers

Uncommon forms of RCC and rare diseases associated with the development of kidney tumors were also discussed at the meeting. Eric Jonasch of MD Anderson Cancer Center, who runs one of the world's only von Hippel-Lindau clinics that focuses on a multidisciplinary approach to treating the kidney tumors and other manifestations of the disease, presented the results of a phase II study of pazopanib in patients with von Hippel-Lindau disease (VHL). This study—the largest prospective VHL-

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specific study to dates—included 32 patients with confirmed VHL and evaluated the ability of pazopanib to shrink lesions associated with the disease. Of the 31 evaluable patients in the study, 18 exhibited stable disease, while 13 had confirmed responses. None had progressive disease. Dose reductions were required in 12 patients and 8 patients had adverse events requiring discontinuation of the treatment (4 due to transaminitis). These results suggest that pazopanib may be an alternative to surgical intervention in some VHL cases.[16]

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