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A SPECIAL MEETING REVIEW EDITION

Highlights in Renal Cell Carcinoma From the Sixteenth International Kidney Cancer Symposium

A Review of Selected Presentations From the Sixteenth International Kidney Cancer Symposium • November 3-4, 2017 • Miami, Florida

Special Reporting on:

- VEGF Tyrosine Kinase Inhibitors/Immunotherapy Combinations Will Become the Standard of Care Soon
- Non–Clear Cell Renal Cell Carcinoma
- Ipilimumab/Nivolumab Is the New Standard of Care in Metastatic Renal Cell Carcinoma
- How Should We Treat Brain Metastases From Renal Cell Carcinoma?
- Guidelines on Managing Small Renal Masses: Compare and Contrast
- Imaging in Renal Cell Carcinoma: Novel Methods and Approaches
- A Perspective on Adjuvant Renal Cell Carcinoma Trials
- Axitinib and Cabozantinib in the Treatment of Sunitinib-Refractory Patients With Metastatic Renal Cell Carcinoma: Results of Matching Adjusted Indirect Treatment Comparison Analysis of the AXIS and METEOR Trials
- Nivolumab in the CheckMate 374, CheckMate 016, and CheckMate 025 Trials

PLUS Meeting Abstract Summaries

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POWER FORWARD

WITH CABOMETYX® (cabozantinib)

First and only TKI to surpass the efficacy of sunitinib in advanced RCC[1]

CABOSUN: A head-to-head, randomized (1:1), open-label, multicenter trial of CABOMETYX (n=79) 60 mg administered orally once daily or sunitinib (n=78) 50 mg administered orally once daily on a schedule of 4 weeks on treatment followed by 2 weeks off in first-line patients with advanced RCC, conducted by a cooperative group in the US. Patients had to have intermediate- or poor-risk disease, as defined by IMDC risk categories, clear-cell component, measurable disease, and ECOG PS 0-2. The primary endpoint was PFS. Secondary endpoints included ORR, OS, and safety. Stratification was based on IMDC risk and presence or absence of bone metastases.[1-3]

INDICATION

CABOMETYX® (cabozantinib) is indicated for the treatment of patients with advanced renal cell carcinoma (RCC).

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage: Severe and fatal hemorrhages have occurred with CABOMETYX. In RCC trials, the incidence of Grade ≥3 hemorrhagic events was 3% in CABOMETYX patients. Do not administer CABOMETYX to patients that have or are at risk for severe hemorrhage.

Gastrointestinal (GI) Perforations and Fistulas: In RCC trials, GI perforations were reported in 1% of CABOMETYX patients. Fatal perforations occurred in patients treated with CABOMETYX. In RCC studies, fistulas were reported in 1% of CABOMETYX patients. Monitor patients for symptoms of perforations and fistulas, including abscess and sepsis. Discontinue CABOMETYX in patients who experience a GI perforation or a fistula that cannot be appropriately managed.

Thrombotic Events: Thrombotic events increased with CABOMETYX. In RCC trials, venous thromboembolism occurred in 9% (including 5% pulmonary embolism) and arterial thromboembolism occurred in 1% of CABOMETYX patients. Fatal thrombotic events occurred in the cabozantinib clinical program. Discontinue CABOMETYX in patients who develop an acute myocardial infarction or any other arterial thromboembolic complication.

Hypertension and Hypertensive Crisis: Treatment-emergent hypertension, including hypertensive crisis, increased with CABOMETYX. In RCC trials, hypertension was reported in 44% (18% Grade ≥3) of CABOMETYX patients. Monitor blood pressure prior to initiation and regularly during CABOMETYX treatment. Withhold CABOMETYX for hypertension that is not adequately controlled with medical management; when controlled, resume CABOMETYX at a reduced dose. Discontinue CABOMETYX if there is evidence of hypertensive crisis or for severe hypertension that cannot be controlled with antihypertensive therapy or medical management.

Diarrhea: In RCC trials, diarrhea occurred in 74% of CABOMETYX patients. Grade 3 diarrhea occurred in 11% of CABOMETYX patients. Withhold CABOMETYX in patients who develop intolerable Grade 2 diarrhea or Grade 3-4 diarrhea that cannot be managed with standard antidiarrheal treatments until improvement to Grade 1; resume CABOMETYX at a reduced dose.

EXELIXIS®

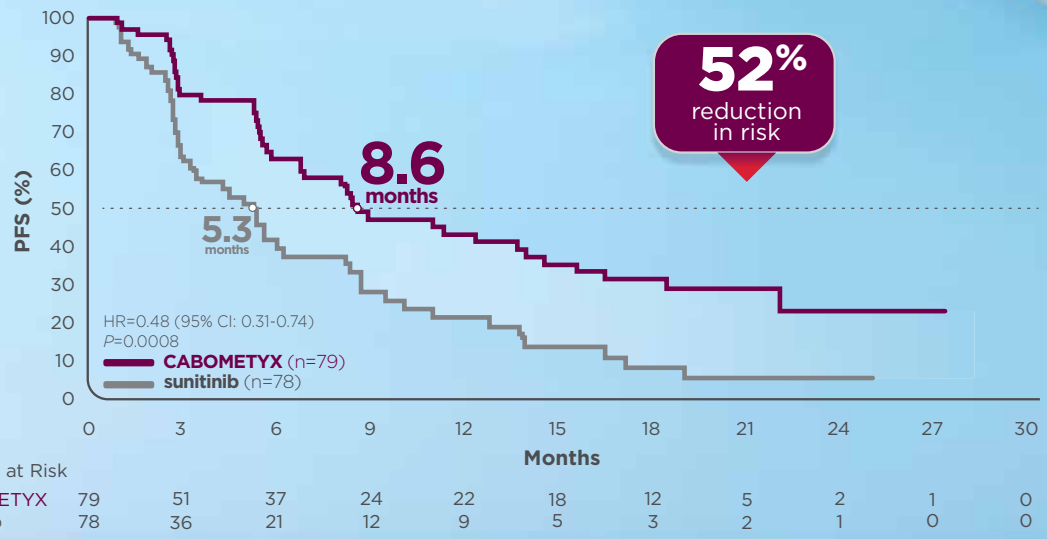
CA-0604 01/18

NOW APPROVED

IN FIRST-LINE ADVANCED RCC

CABOMETYX demonstrated a statistically significant improvement in median PFS vs sunitinib[1]*

PRIMARY ENDPOINT: PFS



Patients at Risk

CABOMETYX	79	51	37	24	22	18	12	5	2	1	0
sunitinib	78	36	21	12	9	5	3	2	1	0	0

No new safety signals were observed with CABOMETYX in the CABOSUN trial[1]

- **The CABOSUN safety profile was generally consistent with that of the initial CABOMETYX product approval**
- **The most commonly reported (≥25%) adverse reactions are: diarrhea, fatigue, nausea, decreased appetite, hypertension, PPE, weight decreased, vomiting, dysgeusia, and stomatitis**

*PFS was assessed by a retrospective blinded IRRC.[1]

CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; HR=hazard ratio; IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; IRRC=independent radiology review committee; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PPE=palmar-plantar erythrodysesthesia; PS=performance status; RCC=renal cell carcinoma; TKI=tyrosine kinase inhibitor.

Palmar-Plantar Erythrodysesthesia (PPE): In RCC trials, PPE occurred in 42% of CABOMETYX patients. Grade 3 PPE occurred in 8% of CABOMETYX patients. Withhold CABOMETYX in patients who develop intolerable Grade 2 PPE or Grade 3 PPE until improvement to Grade 1; resume CABOMETYX at a reduced dose.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS): RPLS, a syndrome of subcortical vasogenic edema diagnosed by characteristic finding on MRI, occurred in the cabozantinib clinical program. Evaluate for RPLS in patients presenting with seizures, headache, visual disturbances, confusion, or altered mental function. Discontinue CABOMETYX in patients who develop RPLS.

Embryo-fetal Toxicity: CABOMETYX can cause fetal harm. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during CABOMETYX treatment and for 4 months after the last dose.

ADVERSE REACTIONS

The most commonly reported (≥25%) adverse reactions were: diarrhea, fatigue, nausea, decreased appetite, hypertension, PPE, weight decreased, vomiting, dysgeusia, and stomatitis.

DRUG INTERACTIONS

Strong CYP3A4 Inhibitors: If concomitant use with strong CYP3A4 inhibitors cannot be avoided, reduce the CABOMETYX dosage.

Strong CYP3A4 Inducers: If concomitant use with strong CYP3A4 inducers cannot be avoided, increase the CABOMETYX dosage.

USE IN SPECIFIC POPULATIONS

Lactation: Advise women not to breastfeed while taking CABOMETYX and for 4 months after the final dose.

Hepatic Impairment: In patients with mild to moderate hepatic impairment, reduce the CABOMETYX dosage. CABOMETYX is not recommended for use in patients with severe hepatic impairment.

Please see Brief Summary of the Prescribing Information for CABOMETYX on adjacent pages.

References: 1. CABOMETYX® (cabozantinib) Prescribing Information. Exelixis, Inc, 2017. **2.** Choueiri TK, Halabi S, Sanford BL, et al. Cabozantinib versus sunitinib as initial targeted therapy for patients with metastatic renal cell carcinoma of poor or intermediate risk: the Alliance A031203 CABOSUN trial. *J Clin Oncol*. 2017;35(6):591-597. **3.** Data on file. Exelixis, Inc.

Learn more at CABOMETYX.com

CABOMETYX®
(cabozantinib) tablets
60 mg | 40 mg | 20 mg

CABOMETYX™ (CABOZANTINIB) TABLETS

BRIEF SUMMARY OF PRESCRIBING INFORMATION.
PLEASE SEE THE CABOMETYX PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION.
INITIAL U.S. APPROVAL: 2012

1 INDICATIONS AND USAGE

CABOMETYX is indicated for the treatment of patients with advanced renal cell carcinoma (RCC).

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hemorrhage

Severe and fatal hemorrhages have occurred with CABOMETYX. In two RCC studies, the incidence of Grade ≥ 3 hemorrhagic events was 3% in CABOMETYX-treated patients.

Do not administer CABOMETYX to patients that have or are at risk for severe hemorrhage.

5.2 GI Perforations and Fistulas

In RCC studies, fistulas were reported in 1% of CABOMETYX-treated patients. Fatal perforations occurred in patients treated with CABOMETYX. In RCC studies, gastrointestinal (GI) perforations were reported in 1% of CABOMETYX-treated patients.

Monitor patients for symptoms of fistulas and perforations, including abscess and sepsis. Discontinue CABOMETYX in patients who experience a fistula which cannot be appropriately managed or a GI perforation.

5.3 Thrombotic Events

CABOMETYX treatment results in an increased incidence of thrombotic events. In RCC studies, venous thromboembolism occurred in 9% (including 5% pulmonary embolism) and arterial thromboembolism occurred in 1% of CABOMETYX-treated patients. Fatal thrombotic events occurred in the cabozantinib clinical program.

Discontinue CABOMETYX in patients who develop an acute myocardial infarction or any other arterial thromboembolic complication.

5.4 Hypertension and Hypertensive Crisis

CABOMETYX treatment results in an increased incidence of treatment-emergent hypertension, including hypertensive crisis. In RCC studies, hypertension was reported in 44% (18% Grade ≥ 3) of CABOMETYX-treated patients. Monitor blood pressure prior to initiation and regularly during CABOMETYX treatment. Withhold CABOMETYX for hypertension that is not adequately controlled with medical management; when controlled, resume CABOMETYX at a reduced dose. Discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy. Discontinue CABOMETYX if there is evidence of hypertensive crisis or severe hypertension despite optimal medical management.

5.5 Diarrhea

In RCC studies, diarrhea occurred in 74% of patients treated with CABOMETYX. Grade 3 diarrhea occurred in 11% of patients treated with CABOMETYX. Withhold CABOMETYX in patients who develop intolerable Grade 2 diarrhea or Grade 3-4 diarrhea that cannot be managed with standard antidiarrheal treatments until improvement to Grade 1; resume CABOMETYX at a reduced dose.

5.6 Palmar-Plantar Erythrodysesthesia

In RCC studies, palmar-plantar erythrodysesthesia (PPE) occurred in 42% of patients treated with CABOMETYX. Grade 3 PPE occurred in 8% of patients treated with CABOMETYX. Withhold CABOMETYX in patients who develop intolerable Grade 2 PPE or Grade 3 PPE until improvement to Grade 1; resume CABOMETYX at a reduced dose.

5.7 Reversible Posterior Leukoencephalopathy Syndrome

Reversible Posterior Leukoencephalopathy Syndrome (RPLS), a syndrome of subcortical vasogenic edema diagnosed by characteristic finding on MRI, occurred in the cabozantinib clinical program. Perform an evaluation for RPLS in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function. Discontinue CABOMETYX in patients who develop RPLS.

5.8 Embryo-fetal Toxicity

Based on data from animal studies and its mechanism of action, CABOMETYX can cause fetal harm when administered to a pregnant woman. Cabozantinib administration to pregnant animals during organogenesis resulted in embryolethality at exposures below those occurring clinically at the recommended dose, and in increased incidences of skeletal variations in rats and visceral variations and malformations in rabbits. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with CABOMETYX and for 4 months after the last dose.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed above and in the Warnings and Precautions section of the prescribing information: Hemorrhage, GI Perforations and Fistulas, Thrombotic Events, Hypertension and Hypertensive Crisis, Diarrhea, Palmar-plantar erythrodysesthesia, Reversible Posterior Leukoencephalopathy Syndrome.

6.1 Clinical Trial Experience

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 practice.

METEOR

The safety of CABOMETYX was evaluated in METEOR, a randomized, open-label trial in which 331 patients with advanced renal cell carcinoma received 60 mg CABOMETYX and 322 patients received 10 mg everolimus administered daily until disease progression or unacceptable toxicity. Patients on both arms who had disease progression could continue treatment at the discretion of the investigator. The median duration of treatment was 7.6 months (range 0.3 – 20.5) for patients receiving CABOMETYX and 4.4 months (range 0.21 – 18.9) for patients receiving everolimus.

Adverse reactions which occurred in ≥ 25% of CABOMETYX-treated patients included, in order of decreasing frequency: diarrhea, fatigue, nausea, decreased appetite, palmar-plantar erythrodysesthesia (PPE), hypertension, vomiting, weight decreased, and constipation. Grade 3-4 adverse reactions and laboratory abnormalities which occurred in ≥ 5% of patients were hypertension, diarrhea, fatigue, PPE, hyponatremia, hypophosphatemia, hypomagnesemia, lymphocytes decreased, anemia, hypokalemia, and GGT increased.

The dose was reduced in 60% of patients receiving CABOMETYX and in 24% of patients receiving everolimus. Twenty percent (20%) of patients received 20 mg CABOMETYX as their lowest dose. The most frequent adverse reactions leading to dose reduction in patients treated with CABOMETYX were: diarrhea, PPE, fatigue, and hypertension. Adverse reactions led to study treatment being held in 70% patients receiving CABOMETYX and in 59% patients receiving everolimus. Adverse reactions led to study treatment discontinuation in 10% of patients receiving CABOMETYX and in 10% of patients receiving everolimus. The most frequent adverse reactions leading to permanent discontinuation in patients treated with CABOMETYX were decreased appetite (2%) and fatigue (1%).

Table 1. Adverse Reactions Occurring in ≥ 10% Patients Who Received CABOMETYX in METEOR

Adverse Reaction	CABOMETYX (n=331)[1]		Everolimus (n=322)	
	All Grades[2]	Grade 3-4	All Grades[2]	Grade 3-4
	Percentage (%) of Patients			
Gastrointestinal Disorders				
Diarrhea	74	11	28	2
Nausea	50	4	28	<1
Vomiting	32	2	14	<1
Stomatitis	22	2	24	2
Constipation	25	<1	19	<1
Abdominal pain[3]	23	4	13	2
Dyspepsia	12	<1	5	0
General Disorders and Administration Site Conditions				
Fatigue	56	9	47	7
Mucosal inflammation	19	<1	23	3
Asthenia	19	4	16	2
Metabolism and Nutrition Disorders				
Decreased appetite	46	3	34	<1
Skin and Subcutaneous Tissue Disorders				
Palmar-plantar erythrodysesthesia	42	8	6	<1
Rash[4]	23	<1	43	<1
Dry skin	11	0	10	0
Vascular Disorders				
Hypertension[5]	39	16	8	3
Investigations				
Weight decreased	31	2	12	0
Nervous System Disorders				
Dysgeusia	24	0	9	0
Headache	11	<1	12	<1
Dizziness	11	0	7	0
Endocrine Disorders				
Hypothyroidism	21	0	<1	<1
Respiratory, Thoracic, and Mediastinal Disorders				
Dysphonia	20	<1	4	0
Dyspnea	19	3	29	4
Cough	18	<1	33	<1
Blood and Lymphatic Disorders				
Anemia	17	5	38	16
Musculoskeletal and Connective Tissue Disorders				
Pain in extremity	14	1	8	<1
Muscle spasms	13	0	5	0
Arthralgia	11	<1	14	1
Renal and Urinary Disorders				
Proteinuria	12	2	9	<1

[1] One subject randomized to everolimus received cabozantinib.
[2] National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0
[3] Includes PT terms abdominal pain, abdominal pain upper, and abdominal pain lower
[4] Includes PT terms rash, rash erythematous, rash follicular, rash macular, rash papular, rash pustular, rash vesicular, genital rash, intermittent leg rash, rash on scrotum and penis, rash maculo-papular, rash pruritic, contact dermatitis, dermatitis acneiform
[5] Includes PT terms hypertension, blood pressure increased, hypertensive crisis, blood pressure fluctuation

Other clinically important adverse reactions (all grades) that were reported in <10% of patients treated with CABOMETYX included: wound complications (2%), convulsion (<1%), pancreatitis (<1%), osteonecrosis of the jaw (<1%), and hepatitis cholestatic (<1%).

Table 2. Laboratory Abnormalities Occurring in ≥ 25% Patients Who Received CABOMETYX in METEOR

Test	CABOMETYX (n=331)		Everolimus (n=322)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
	Percentage (%) of Patients			
Chemistry				
AST increased	74	3	40	<1
ALT increased	68	3	32	<1
Creatinine increased	58	<1	71	0
Triglycerides increased	53	4	73	13
Hypophosphatemia	48	8	36	5
Hyperglycemia	37	2	59	8
Hypoalbuminemia	36	2	28	<1
ALP increased	35	2	29	1
Hypomagnesemia	31	7	4	<1
Hyponatremia	30	8	26	6
GGT increased	27	5	43	9
Hematology				
White blood cells decreased	35	<1	31	<1
Absolute neutrophil count decreased	31	2	17	<1
Hemoglobin decreased	31	4	71	17
Lymphocytes decreased	25	7	39	12
Platelets decreased	25	<1	27	<1

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase.
National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0

CABOSUN

The safety of CABOMETYX was evaluated in CABOSUN, a randomized, open-label trial in patients with advanced renal cell carcinoma, in which 78 patients received 60 mg CABOMETYX daily and 72 patients received 50 mg sunitinib taken once daily (4 weeks on treatment followed by 2 weeks off), until disease progression or unacceptable toxicity. The median duration of treatment was 6.5 months (range 0.2 – 28.7) for patients receiving CABOMETYX and 3.1 months (range 0.2 – 25.5) for patients receiving sunitinib.

Within 30 days of treatment, there were 4 deaths in patients treated with CABOMETYX and 6 deaths in patients treated with sunitinib. Of the 4 patients treated with CABOMETYX, two patients died due to gastrointestinal perforation, one patient had acute renal failure, and one patient died due to clinical deterioration. All Grade 3-4 adverse reactions were collected in the entire safety population. The most frequent Grade 3-4 adverse reactions (≥5%) in patients treated with CABOMETYX were hypertension, diarrhea, hyponatremia, hypophosphatemia, PPE, fatigue, ALT increased, decreased appetite, stomatitis, pain, hypotension, and syncope.

The median average daily dose was 50.3 mg for CABOMETYX and 44.7 mg for sunitinib (excluding scheduled sunitinib non-dosing days). The dose was reduced in 46% of patients receiving CABOMETYX and in 35% of patients receiving sunitinib. The dose was held in 73% of patients receiving CABOMETYX and in 71% of patients receiving sunitinib. Based on patient disposition, 21% of patients receiving CABOMETYX and 22% of patients receiving sunitinib discontinued due to an adverse reaction.

Table 3. Grade 3-4 Adverse Reactions Occurring in ≥ 1% Patients Who Received CABOMETYX in CABOSUN

	CABOZANTINIB (n = 78)	Sunitinib (n = 72)
	Grade 3-4[1]	Grade 3-4[1]
	Percentage (%) of Patients	
Patients with any Grade 3-4 Adverse Reaction	68	65
Gastrointestinal Disorders		
Diarrhea	10	11
Stomatitis	5	6
Nausea	3	4
Vomiting	1	3

	CABOZANTINIB (n = 78)	Sunitinib (n = 72)
	Grade 3-4[1]	Grade 3-4[1]
	Percentage (%) of Patients	
Constipation	1	0
General Disorders and Administration Site Conditions		
Fatigue	6	17
Pain	5	0
Metabolism and Nutrition Disorders		
Hyponatremia[2]	9	8
Hypophosphatemia[2]	9	7
Decreased appetite	5	1
Dehydration	4	1
Hypocalcemia[2]	3	0
Hypomagnesemia[2]	3	0
Hyperkalemia[2]	1	3
Skin and Subcutaneous Skin Disorders		
Palmar-plantar erythrodysesthesia	8	4
Skin ulcer	3	0
Vascular Disorders		
Hypertension[3]	28	21
Hypotension	5	1
Angiopathy	1	1
Investigations		
ALT increased[2]	5	0
Weight decreased	4	0
AST increased[2]	3	3
Blood creatinine increased[2]	3	3
Lymphocyte count decreased[2]	1	6
Platelet count decreased[2]	1	11
Nervous System Disorders		
Syncope	5	0
Respiratory, Thoracic, and Mediastinal Disorders		
Dyspnea	1	6
Dysphonia	1	0
Blood and Lymphatic Disorders		
Anemia	1	3
Psychiatric Disorders		
Depression	4	0
Confusional state	1	1
Infections and Infestations		
Lung infection	4	0
Musculoskeletal and Connective Tissue Disorders		
Back pain	4	0
Bone pain	3	1
Pain in extremity	3	0
Arthralgia	1	0
Renal and Urinary Disorders		
Renal failure acute	4	1
Proteinuria	3	1

ALT, alanine aminotransferase; AST, aspartate aminotransferase

[1] National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0

[2] Laboratory abnormalities are reported as adverse reactions and not based on shifts in laboratory values

[3] Includes PT term hypertensions

7 DRUG INTERACTIONS

Table 4. Clinically Significant Drug Interactions Involving Drugs that Affect Cabozantinib

Strong CYP3A4 Inhibitors	
Clinical Implications:	• Concomitant use of CABOMETYX with a strong CYP3A4 inhibitor increased the exposure of cabozantinib compared to the use of CABOMETYX alone. • Increased cabozantinib exposure may increase the risk of exposure-related toxicity.
Prevention or Management:	Reduce the dosage of CABOMETYX if concomitant use with strong CYP3A4 inhibitors cannot be avoided.
Examples:	Boceprevir, clarithromycin, conivaptan, grapefruit juice[a], indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telithromycin, and voriconazole
Strong CYP3A4 Inducers	
Clinical Implications:	• Concomitant use of CABOMETYX with a strong CYP3A4 inducer decreased the exposure of cabozantinib compared to the use of CABOMETYX alone. • Decreased cabozantinib exposure may lead to reduced efficacy.
Prevention or Management:	Increase the dosage of CABOMETYX if concomitant use with strong CYP3A4 inducers cannot be avoided.
Examples:	Rifampin, phenytoin, carbamazepine, phenobarbital, rifabutin, rifapentine, and St. John's Wort[b]

[a] The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (e.g., high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (e.g., low dose, single strength).

[b] The effect of St. John's Wort varies widely and is preparation-dependent

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action, CABOMETYX can cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. In animal developmental and reproductive toxicology studies administration of cabozantinib to pregnant rats and rabbits during organogenesis resulted in embryofetal lethality and structural anomalies at exposures that were below those occurring clinically at the recommended dose. Advise pregnant women or women of childbearing potential of the potential hazard to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In an embryo-fetal development study in pregnant rats, daily oral administration of cabozantinib throughout organogenesis caused increased embryo-fetal lethality compared to controls at a dose of 0.03 mg/kg (approximately 0.12-fold of human AUC at the recommended dose). Findings included delayed ossification and skeletal variations at a dose of 0.01 mg/kg/day (approximately 0.04-fold of human AUC at the recommended dose).

In pregnant rabbits, daily oral administration of cabozantinib throughout organogenesis resulted in findings of visceral malformations and variations including reduced spleen size and missing lung lobe at 3 mg/kg (approximately 1.1-fold of the human AUC at the recommended dose).

In a pre- and postnatal study in rats, cabozantinib was administered orally from gestation day 10 through postnatal day 20. Cabozantinib did not produce adverse maternal toxicity or affect pregnancy, parturition or lactation of female rats, and did not affect the survival, growth or postnatal development of the offspring at doses up to 0.3 mg/kg/day (0.05-fold of the maximum recommended clinical dose).

8.2 Lactation

Risk Summary

There is no information regarding the presence of cabozantinib or its metabolites in human milk, or their effects on the breastfed infant, or milk production. Because of the potential for serious adverse reactions in a breastfed infant from CABOMETYX, advise a lactating woman not to breastfeed during treatment with CABOMETYX and for 4 months after the final dose.

8.3 Females and Males of Reproductive Potential

Contraception

Females

CABOMETYX can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with CABOMETYX and for 4 months after the final dose.

Infertility

Females and Males

Based on findings in animals, CABOMETYX may impair fertility in females and males of reproductive potential.

8.4 Pediatric Use

The safety and effectiveness of CABOMETYX in pediatric patients have not been established.

Juvenile Animal Data

Juvenile rats were administered cabozantinib daily at doses of 1 or 2 mg/kg/day from Postnatal Day 12 (comparable to less than 2 years in humans) through Postnatal Day 35 or 70. Mortalities occurred at doses equal and greater than 1 mg/kg/day (approximately 0.16 times the clinical dose of 60 mg/day based on body surface area). Hypoactivity was observed at both doses tested on Postnatal Day 22. Targets were generally similar to those seen in adult animals, occurred at both doses, and included the kidney (nephropathy, glomerulonephritis), reproductive organs, gastrointestinal tract (cystic dilatation and hyperplasia in Brunner's gland and inflammation of duodenum; and epithelial hyperplasia of colon and cecum), bone marrow (hypocellularity and lymphoid depletion), and liver. Tooth abnormalities and whitening as well as effects on bones including reduced bone mineral content and density, physeal hypertrophy, and decreased cortical bone also occurred at all dose levels. Recovery was not assessed at the 2 mg/kg dose level (approximately 0.32 times the clinical dose of 60 mg based on body surface area) due to high levels of mortality. At the low dose level, effects on bone parameters were partially resolved but effects on the kidney and epididymis/testis persisted after treatment ceased.

8.5 Geriatric Use

In RCC studies, 41% of patients treated with CABOMETYX were age 65 years and older, and 8% of patients were 75 years and older.

Grade 3-4 adverse reactions occurred in 73% of patients age 65 years and older, and in 76% of patients 75 years and older. No overall differences in safety or efficacy were observed between older and younger patients.

8.6 Hepatic Impairment

Increased exposure to cabozantinib has been observed in patients with mild to moderate hepatic impairment. Reduce the CABOMETYX dose in patients with mild (Child-Pugh score (C-P) A) or moderate (C-P B) hepatic impairment. CABOMETYX is not recommended for use in patients with severe hepatic impairment.

8.7 Renal Impairment

Dosage adjustment is not required in patients with mild or moderate renal impairment. There is no experience with CABOMETYX in patients with severe renal impairment.

10 OVERDOSAGE

One case of overdosage was reported in the cabozantinib clinical program; a patient inadvertently took twice the intended dose (200 mg daily) of another formulation of cabozantinib product for nine days. The patient suffered Grade 3 memory impairment, Grade 3 mental status changes, Grade 3 cognitive disturbance, Grade 2 weight loss, and Grade 1 increase in BUN. The extent of recovery was not documented.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Inform patients of the following:

Hemorrhage: Instruct patients to contact their healthcare provider to seek immediate medical attention for signs or symptoms of unusual severe bleeding or hemorrhage.

Gastrointestinal disorders: Advise patients that gastrointestinal disorders such as diarrhea, nausea, vomiting, and constipation may develop during CABOMETYX treatment and to seek immediate medical attention if they experience persistent or severe abdominal pain because cases of gastrointestinal perforation and fistula have been reported in patients taking CABOMETYX.

Thrombotic Events: Venous and arterial thrombotic events have been reported. Advise patients to report signs or symptoms of an arterial thrombosis. Venous thromboembolic events including pulmonary embolus have been reported. Advise patients to contact their health care provider if new onset of dyspnea, chest pain, or localized limb edema occurs.

Hypertension: Inform patients of the signs and symptoms of hypertension. Advise patients to undergo routine blood pressure monitoring and to contact their health care provider if blood pressure is elevated or if they experience signs or symptoms of hypertension.

Diarrhea: Advise patients to notify their healthcare provider at the first signs of poorly formed or loose stool or an increased frequency of bowel movements.

Palmar-plantar erythrodysesthesia: Advise patients to contact their healthcare provider for progressive or intolerable rash.

Wound healing: Patients should be advised to contact their healthcare provider before any planned surgeries, including dental surgery.

Drug interactions: Advise patients to inform their healthcare provider of all prescription or nonprescription medication or herbal products that they are taking.

Embryo-fetal toxicity: Advise females of reproductive potential of the potential risk to a fetus. Advise females to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, during treatment with CABOMETYX.

Females of reproductive potential: Advise patients of reproductive potential to use effective contraception during treatment with CABOMETYX and for at least four months after the final dose of CABOMETYX.

Lactation: Advise women not to breastfeed during treatment with CABOMETYX and for 4 months following the last dose.

Important Administration Information

- Instruct patients not to eat for at least 2 hours before and at least 1 hour after taking CABOMETYX. Instruct patients to not crush CABOMETYX tablets and to take CABOMETYX tablets with a full glass (at least 8 ounces) of water.
- Advise patients not to consume grapefruits or grapefruit juice while taking CABOMETYX.

This brief summary is based on the CABOMETYX Prescribing Information Revision 12/2017
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VEGF Tyrosine Kinase Inhibitors/Immunotherapy Combinations Will Become the Standard of Care Soon

Dr Tian Zhang presented an overview of treatment with immunotherapy in combination with inhibitors of the vascular endothelial growth factor (VEGF) among patients with renal cell carcinoma (RCC).[1] In tumors of the kidney, the presence of tumor-infiltrating lymphocytes that express programmed death 1 (PD-1) protein is associated with a worse prognosis.[2] Unsupervised gene expression clustering of localized clear cell RCC tumors recently revealed an immune-regulated cluster that was associated with aggressive histologic features and a high risk of disease progression after nephrectomy.[3] These tumors harbored tumor-infiltrating lymphocytes that expressed CD8, PD-1, Tim-3, and Lag-3, as well as CD4-positive and ICOS-positive cells that have a T-regulatory phenotype (such as $CD25^{+}CD127^{-}$ $Foxp3^{+}/Helios^{+}GITR^{+}$). The VEGF inhibitors have been associated with immunomodulatory effects. Treatment with cabozantinib, a tyrosine kinase inhibitor (TKI) that is directed against the VEGF receptor 2, AXL, and MET, has decreased T-regulatory cells in patients with urothelial cancer (P=.015), through a mechanism involving inhibition of Foxp3 (Figure 1).[4] In a retrospective analysis of patients in the phase 3 S-TRAC trial (A Clinical Trial Comparing Efficacy and Safety of Sunitinib Versus Placebo for the Treatment of Patients at High Risk of Recurrent Renal Cell Cancer), outcomes in patients with high-risk RCC were assessed according to results from immunohistochemical staining of PD-L1, CD4, CD8, and CD68 in nephrectomy specimens.[5] Patients with a CD8-positive T-cell density above the median had a longer disease-free survival than patients with a density below the median (not reached vs 3.47 years; hazard ratio [HR], 0.40; 95% CI, 0.20-0.81; P=.009). In contrast, no difference was observed with placebo treatment based on CD8-positive T-cell density (HR, 0.80; 95% CI, 0.42-1.50; P=.484).

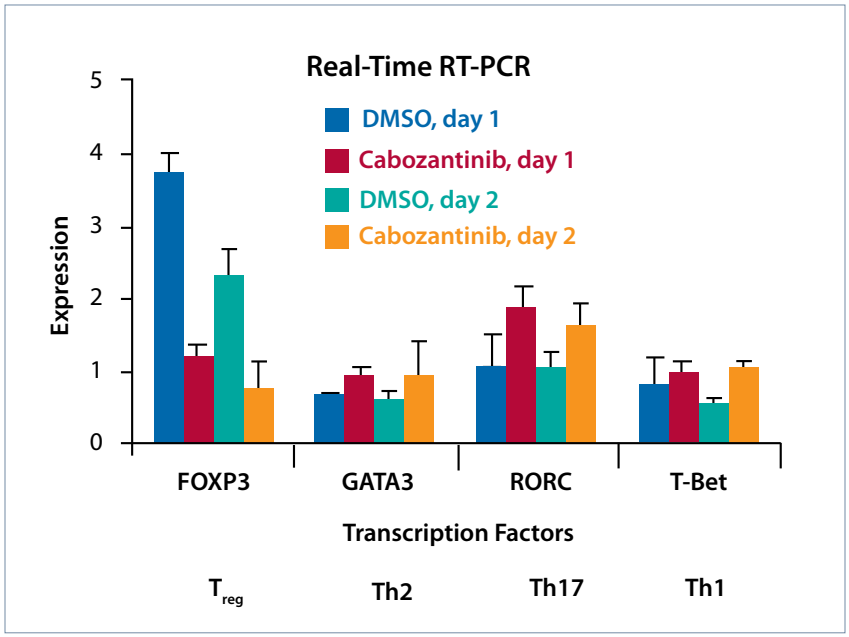

Figure 1. Cabozantinib downregulates the T_{reg} population by acting on T-cell polarization via inhibition of FOXP3. DMSO, dimethyl sulfoxide; RT-PCR, reverse transcription polymerase chain reaction; Th, T helper; T_{reg}, regulatory T cells. Adapted from Apolo AB et al. ASCO abstract 4501. *J Clin Oncol.* 2014;32(5 suppl).[4]

Recent clinical trials have evaluated TKIs in renal cell carcinoma, leading to new management options. In late December 2017, the US Food and Drug Administration (FDA) expanded the approval of cabozantinib to include first-line treatment of patients with advanced renal cell carcinoma. Approval was based on results from the CABOSUN study (Cabozantinib-S-Malate or Sunitinib Malate in Treating Patients With Previously Untreated Locally Advanced or Metastatic Kidney Cancer). This study randomly assigned patients with untreated metastatic RCC to receive cabozantinib or sunitinib.[6] Progression-free survival (PFS) was 8.6 months with cabozantinib vs 5.3 months with sunitinib (HR, 0.48; 95% CI, 0.31-0.74; P=.0008; Table 1). The objective response rate (ORR) was 20% with cabozantinib vs 9% with sunitinib. In the phase 3 CheckMate 214 trial (Nivolumab Combined With Ipilimumab Versus Sunitinib in Previously Untreated Advanced or Metastatic Renal Cell Carcinoma), patients with metastatic RCC were randomly assigned to receive nivolumab plus ipilimumab or sunitinib monotherapy.[7] Median PFS was approximately 12 months for both arms (HR, 0.98; 99.1% CI, 0.79-1.23; P=.8498), with confirmed ORRs of 39% (95% CI, 35%-43%) among patients treated with nivolumab plus ipilimumab and 32% (95% CI, 28%-36%) among those treated with sunitinib.

Results from early-phase clinical trials investigating the combination of VEGF TKIs plus PD-1 or PD

ligand 1 (L1) checkpoint inhibitors in patients with metastatic RCC are now available. Disease control rates ranged from 78% to 100%. [8-13] Most of the reported ORRs ranged from 58% to 83%. Exceptions included the regimen of bevacizumab plus atezolizumab, which yielded an ORR of 32%, and the combination of cabozantinib, ipilimumab, and nivolumab, which had an ORR of 33% (this trial enrolled patients with any metastatic genitourinary malignancy).[12,13] Durable responses were also observed in many of the patients.[9,11] The common toxicities were those most often associated with VEGF TKIs, and included diarrhea, hypertension, fatigue, and hand-foot syndrome. Most grade 3/4 adverse events (AEs) were observed in fewer than 10% of patients, with the exceptions of hypertension, neutropenia, and increased lipase levels.

The combination of a VEGF TKI plus immunotherapy enables the targeting of multiple drivers of tumorigenesis and disease progression, and early-stage trials suggest that response rates are higher than those observed in trials of VEGF TKI monotherapy. Responses with combination treatment may also be more durable. However, combination therapy may have some disadvantages. Treatment has not been defined for patients who developed progressive disease during treatment with a VEGF TKI plus immunotherapy. It will be necessary to investigate optimal sequencing of different VEGF TKIs and checkpoint inhibitors. It is not known whether the high response rates observed in early-phase clinical trials will yield higher rates of PFS and overall survival (OS). Questions that must be resolved include how to measure outcomes against older controls and how to determine when to stop treatment of patients with a complete response (CR). Other issues include management of toxicities and identification of biomarkers for improved patient selection.

Table 1. Updated Outcomes in the CABOSUN Trial of Cabozantinib vs Sunitinib

	Cabozantinib (n=79)	Sunitinib (n=78)
Progression-Free Survival		
Median PFS, months	8.6	5.3
Stratified HR, 95% CI	0.48 (0.31-0.74)	
P value	.0008 (2-sided)	
Tumor Response		
Objective response rate (%),[a] 95% CI	20 (12-31)	9 (4-18)
Disease control rate (%)[b]	75	47
Progressive disease (%)[c]	18	29
Not evaluable or missing (%)	8	23
Any Reduction in Target Lesions (%)	80	50

[a] All responses were partial, except for 1 complete response with cabozantinib for both investigator assessments, and 1 complete response with sunitinib for the original investigator assessment.

[b] Defined as complete response, partial response, or stable disease.

[c] Patients in whom progressive disease was the best overall response.

CABOSUN, Cabozantinib-S-Malate or Sunitinib Malate in Treating Patients With Previously Untreated Locally Advanced or Metastatic Kidney Cancer; PFS, progression-free survival.

Data from Choueiri TK et al. ESMO abstract LBA38. *Ann Oncol.* 2017;28(suppl 5).[6]

ABSTRACT SUMMARY Integrated Biomarker Analysis for 412 Renal Cell Cancer Patients Treated on the Phase 3 COMPARZ Trial: Correlated Common Mutation Events in PBRM1 and BAP1 With Angiogenesis Expression Signatures and Outcomes on Tyrosine Kinase Inhibitor Therapy

The phase 3 COMPARZ trial (Pazopanib Versus Sunitinib in the Treatment of Locally Advanced and/or Metastatic Renal Cell Carcinoma) randomly assigned patients to treatment with pazopanib (800 mg daily) or sunitinib (50 mg daily). Dr Martin Voss presented results from an integrated biomarker analysis performed on samples from patients in COMPARZ with advanced or metastatic clear cell RCC. Tumor RNA was available for 412 patients, tumor DNA was available for 377 patients, and both DNA and RNA were available for 352 patients. Among 174 patients treated with pazopanib, 17.8% had a *BAP1* mutation and 43.1% had a *PBRM1* mutation. *PBRM1* mutations were more common in patients who achieved an objective response to treatment than in those with disease progression (*P*=.012). Both PFS (*P*=.0083) and OS (*P*=.0039) were superior in patients with a *PBRM1* mutation. In contrast, the presence of a *BAP1* mutation was not associated with improved PFS (*P*=.0582) or OS (*P*=.0116). Angiogenesis scores were significantly different in patients with a best response of PR vs stable disease vs progressive disease (*P*=.027). PFS and OS were longer among patients with an RNA angiogenesis score at or above the median compared with those who had a lower score. PFS was 11.24 months vs 8.31 months (*P*=.0023), and OS was 35.48 months vs 26.12 months (*P*=.0058).

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Non–Clear Cell Renal Cell Carcinoma

Variants of RCC differ in terms of clinical behavior, prognosis, and response to systemic therapy.[1] Dr Pavlos Msaouel presented an overview of renal medullary carcinoma, one of the most aggressive RCC subtypes.[2] Renal medullary carcinoma occurs most commonly in patients with sickle cell hemoglobinopathies. Most patients present with metastatic disease, and two-thirds are male.[1] Guidelines for the diagnosis and treatment of renal medullary carcinoma have been proposed.[3] Treatment with anti-VEGF TKIs has not been successful in these patients. Cytotoxic chemotherapy has an ORR of approximately 29%, but responses are typically brief, and few patients survive past 2 years. Radical nephrectomy should be considered in patients with good performance status and low metastatic burden, and in those who respond to systemic therapy. *SMARCB1* is a tumor suppressor gene that has been implicated in the development of renal medullary carcinoma. *SMARCB1* was inactivated in all 5 specimens in a series of renal medullary carcinoma tumors.[4] Four of the cases had developed in patients with sickle cell disease, and in these patients, interchromosomal balanced translocations accounted for *SMARCB1* gene inactivation. Sickle cell disease is associated with reduced interstitial osmolality in the inner medulla, which may contribute to an environment that favors *SMARCB1* deletion and/or translocation.

Dr Gabriel Malouf presented an update on collecting duct carcinoma, another rare and aggressive type of RCC.[5] In a study of 20 archival cases of collecting duct RCC, the complete loss of SMARCB1/INI1

ABSTRACT SUMMARY Genomic Heterogeneity and the Small Renal Mass

Dr Brian Shuch provided data from a prospective study evaluating genomic heterogeneity in small tumors in a consecutive series of patients with nephrectomized clear cell RCC. Included tumors were classified as cT1a (≤4 cm; n=23) or large (≥7 cm; n=24). Nonnecrotic areas were sampled, and DNA and RNA were extracted to examine copy number variations (CNV) and gene signatures. Large tumors showed a higher median number of CNV events (6.5 vs 2.5; *P*=.006). Results were supported by findings from The Cancer Genome Atlas. The median number of subclonal CNVs were also more common in large tumors (3 vs 0; *P*=.002). Small and large tumors were classified based on gene expression profiles. Among mixed A/B tumors, the median number of CNV events was higher for clear cell B regions vs clear cell A regions (7 vs 2; *P*=.041). Intrasample correlation differed by tumor size (*P*=.004), and small tumors exhibited gene expression profiles that were similar to established clear cell A, B, or papillary profiles. These findings support the use of renal mass biopsy with genomic characterization before active surveillance in patients with small tumors.

expression was observed in 15% of cases.[6] A recent analysis from the National Cancer Database showed that 71% of patients with collecting duct RCC presented with metastatic disease, and the median survival was 13 months after diagnosis.[7] Among 184 patients with metastatic collecting duct RCC, improved outcomes were observed in those who underwent both cytoreductive nephrectomy and chemoradiation compared with cytoreductive nephrectomy alone (HR, 0.51; 95% CI, 0.32-0.79). In an unpublished study of 29 patients with collecting duct RCC, a worse outcome was seen in those with metastatic disease and those older than 40 years. Genomic studies suggest an overlap between collecting duct RCC, unclassified RCC, renal medullary carcinoma, and papillary type II RCC. Transcriptome sequencing revealed a unique signature characterized by immunogenic and metabolic aberrations for collecting duct RCC compared with other RCC subtypes.[8] Collecting duct RCC tumors are infiltrated with high levels of CD8-positive lymphocytes; therefore, targeting immunological checkpoints may be an option in this setting. In a recent study, loss of CDKN2A expression was observed in 62.5% of patients with collecting duct RCC, providing a potential pathway for the development of targeted therapies.[9]

Dr James Hsieh discussed unclassified RCC, which represents approximately 5% of RCC cases.[10] Treatments for metastatic clear cell RCC have advanced markedly in the last decade, particularly with the recent approval of cabozantinib, lenvatinib, and nivolumab.[11] However, no standard therapy exists for treatment of unclassified RCC. The development of new treatments has been limited by a lack of knowledge regarding the molecular features of unclassified RCC. To address this limitation, a study was conducted to identify molecular characteristics of unclassified RCC tumors.[12] Targeted next-generation sequencing of 230 oncogenes, tumor suppressor genes, and components of pathways considered candidates for targeted therapy was used to evaluate 62 high-grade primary unclassified RCC tumors. The study identified recurrent somatic mutations in 29 genes, including *NF2* (18%), *BAP1* (13%), *KMT2C* (10%), and *MTOR* (8%). Integrated analysis revealed distinct molecular attributes that characterized 76% of the unclassified RCC tumors, including distinct profiles for subsets of patients with a better or worse clinical outcome. *NF2* is a key mediator of cell-cell contact inhibition and growth factor signaling, and it is involved in the Hippo developmental pathways. Among the 62 tumors, 11 harbored *NF2* mutations, suggesting that the loss of *NF2* expression could characterize an important subset of unclassified RCC tumors. Several lines of evidence showed *NF2* loss in 26% of unclassified RCC cases, along with dysregulated Hippo signaling and YAP activation. *NF2* may act as an early driver of tumorigenesis. Other aberrations identified in the unclassified RCC tumors included mTORC1 hyperactivity, fumarate hydratase deficiency, and defective chromatin modulation. In a study by Casuscelli and colleagues, high-risk features included *TP53* and *PTEN* mutations, as well as imbalanced chromosome duplication (Figure 2).[13]

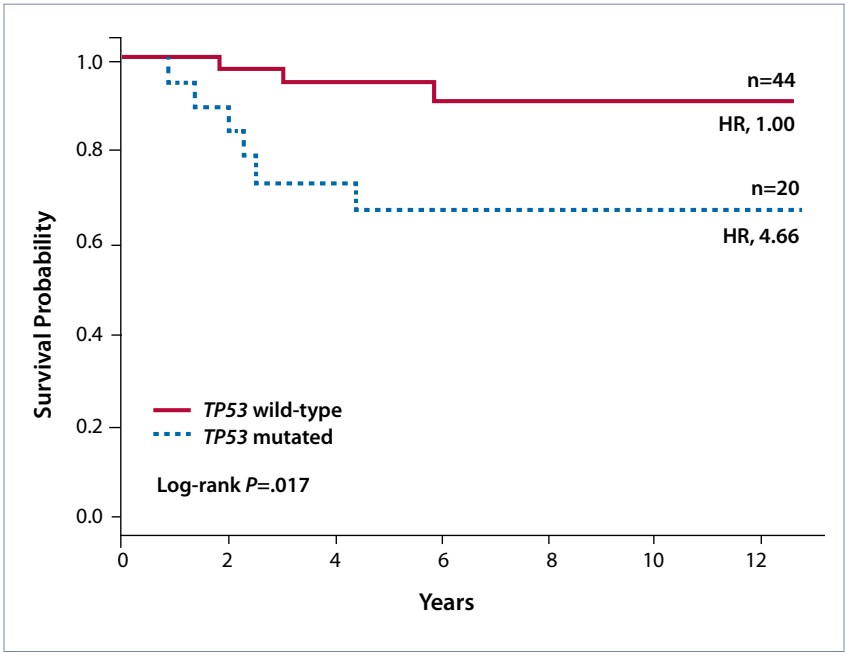

Figure 2. Survival probability according to *TP53* mutational status. HR, hazard ratio. Adapted from Casuscelli J et al. *JCI Insight*. 2017;2(12):92688.[13]

Dr Laurence Albiges discussed papillary RCC, the most common non–clear cell subtype of RCC.[14] The classification includes indolent tumors with multifocal presentation and solitary tumors that are highly aggressive. A retrospective analysis of RCC patients in the International Metastatic Renal Cell Carcinoma Database Consortium identified 5474 patients with metastatic RCC, of whom 5008 (91%) had clear cell RCC and 466 (8.5%) had papillary RCC.[15] In patients with clear cell RCC, OS was 8 months longer, and the HR for death was 0.71. To identify potential molecular targets, 98 frozen papillary RCC samples were assessed using human whole-genome

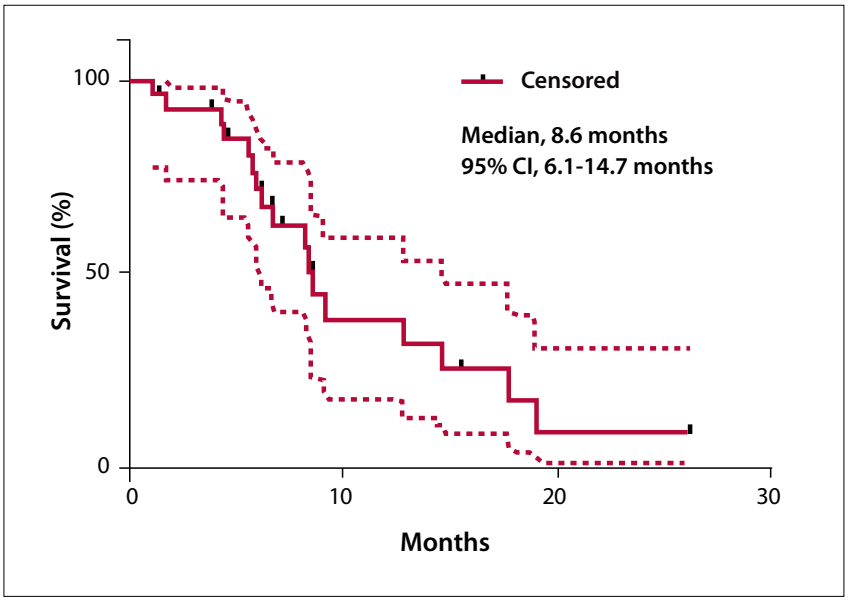

Figure 3. Progression-free survival in a retrospective study of cabozantinib in patients with metastatic variant histology renal cell carcinoma. The dotted lines indicate the 95% CI. Adapted from Campbell MT et al. ESMO abstract 912P. *Ann Oncol*. 2017;28(suppl 5).[19]

arrays.[16] *MET* gene expression was high across all samples. *MET* gene amplification was observed in 81% of type I papillary RCC and 46% of type II papillary RCC tumors, suggesting that MET inhibition may be a potential approach for treating papillary RCC. Eleven mutations (including 4 new ones) in exons 16 to 19 of the *MET* gene were observed in 21.5% of samples. The findings support earlier studies showing strong expression of MET in most papillary RCC tumors.[17] A comprehensive molecular characterization of 161 primary papillary RCC tumors by The Cancer Genome Atlas Research Network showed that type I and type II papillary tumors had different molecular alterations.[18] Type I tumors were characterized by MET alterations, whereas type 2 tumors were characterized by CDKN2A silencing, activation of the NRF2-ARE pathway, and other aberrations.

A retrospective analysis evaluated the efficacy of cabozantinib in patients with non–clear cell RCC who were treated in a phase 3 study.[19] Among 30 patients with metastatic non–clear cell RCC, 17 patients (57%) had papillary RCC. The median age was 58 years (range, 25-81 years), and 87% of patients were male. Prior treatment with a VEGF TKI was reported in 87% of patients. Median PFS among the 30 patients was 8.6 months (95% CI, 6.1-14.7 months; Figure 3). The results suggest that cabozantinib may produce a clinically meaningful benefit in patients with non–clear cell RCC.

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Ipilimumab/Nivolumab Is the New Standard of Care in Metastatic Renal Cell Carcinoma

Dr Brian Rini presented results from the open-label, randomized phase 3 CheckMate 214 trial, which evaluated the combination of ipilimumab plus nivolumab vs sunitinib monotherapy in patients with treatment-naive, advanced or metastatic, clear cell RCC.[1] Results were also presented at the 2017 European Society for Medical Oncology meeting.[2] Patients in the combination arm received nivolumab (3 mg/kg) plus ipilimumab (1 mg/kg) every 3 weeks for 4 doses followed by nivolumab (3 mg/kg) every 2 weeks. Patients in the sunitinib arm received sunitinib (50 mg) once daily for 4 weeks in 6-week cycles. Patients were treated until disease progression or unacceptable toxicity. The primary endpoints of the trial were OS, ORR, and PFS among patients at intermediate to poor risk, who constituted approximately 75% of the entire intent-to-treat population.

Patients had a median age of 61 years, and approximately 73% were male. In the intent-to-treat population, patients were randomly assigned to receive nivolumab plus ipilimumab (n=550) or sunitinib (n=546). Prognostic scores, as assessed by criteria from the International Metastatic Renal Cell Carcinoma Database Consortium, were favorable in 21%, intermediate in 61%, and poor in 18% of patients. Intermediate-risk or poor-risk disease was reported in 425 patients in the combination arm and 422 in the sunitinib monotherapy arm. Among these patients, the confirmed ORR was 42% (95% CI, 37%-47%) in the combination treatment arm and 27% (95% CI, 22%-31%) in the sunitinib arm (P<.0001). The CR rate was 9% in the combination arm vs 1% in the comparator arm, and the partial response (PR) rate was 32% vs 25%. The median duration of response was not reached (95% CI, 21.8 months to not estimable [NE]) in the combination arm vs 18.2 months (95% CI, 14.8 months to NE) in the comparator arm. An ongoing response was reported in 72% in the combination arm vs 63% in the sunitinib arm. Median PFS was 11.6 months (95% CI, 8.7-15.5 months) in patients treated with nivolumab plus ipilimumab vs 8.4 months (95% CI, 7.0-10.8 months) in patients treated with sunitinib (HR, 0.82; 99.1% CI, 0.64-1.05; P=.0331; Figure 4). Median OS was not reached (95% CI, 28.2 months to NE) in the combination treatment arm vs 26.0 months (95% CI, 22.1 months to NE) in the sunitinib arm (HR, 0.63; 99.8% CI, 0.44-0.89; P=.00003).

In the entire study population of 1096 patients, the confirmed ORR was 39% (95% CI, 35%-43%) in the nivolumab plus ipilimumab arm vs 32% (95% CI, 28%-36%) in the sunitinib monotherapy arm (P=.0191). Median PFS was 12.4 months (95% CI, 9.9-16.5 months) in the combination arm vs 12.3 months (95% CI, 9.8-15.2 months) in the comparator arm (HR, 0.98; 99.1% CI, 0.79-1.23; P=.8498). Median OS was not reached (95% CI, NE to NE) in the combination arm vs 32.9 months (95% CI, NE to NE) in the sunitinib arm (HR, 0.68; 99.8% CI, 0.49-0.95; P=.00028). In the subset of 249 patients with favorable-risk disease, the confirmed ORR was 29% (95% CI, 21%-38%) for combination treatment vs 52% (95% CI, 43%-61%) for sunitinib monotherapy (P=.0002). Median PFS was 15.3 months (95% CI, 9.7-20.3 months) for combination treatment vs 25.1 months (95% CI, 20.9 months to NE) for sunitinib (HR, 2.18; 99.1% CI, 1.29-3.68; P<.0001). (ORR and PFS were assessed by Response Evaluation Criteria In Solid Tumors [RECIST] criteria rather than immune-related RECIST criteria.)

Antitumor activity was assessed according to levels of PD-L1. In

ABSTRACT SUMMARY Long-Term Response and Time to Response to Pazopanib (PAZ) and Sunitinib (SUN) in Metastatic Renal Cell Carcinoma (mRCC): COMPARZ Subanalysis

Dr Nizar Tannir presented results from a post hoc analysis of the clinical characteristics of patients in the COMPARZ trial who achieved a CR, PR, or PFS lasting at least 10 months. The analysis also determined the time to response with pazopanib or sunitinib. A CR or PR lasting at least 10 months was reported in 14% of 557 patients in the pazopanib arm and 13% of 553 patients in the sunitinib arm. CRs or PRs lasting 18 months or longer were observed in 6% of pazopanib patients and 7% of sunitinib patients. PFS duration was at least 10 months in 31.4% of patients in the pazopanib arm vs 33.6% in the sunitinib arm. A PFS duration of at least 18 months occurred in 14.2% of patients in the pazopanib arm vs 15.4% of patients in the sunitinib arm. Among patients who achieved a CR or PR, the median time to response was 11.9 weeks (95% CI, 11.3-12.1 weeks) with pazopanib vs 17.4 weeks (95% CI, 12.7-18.0 weeks) with sunitinib. Logistic regression analysis did not identify any baseline patient factors that were significantly associated with a response duration of at least 10 months or at least 18 months.

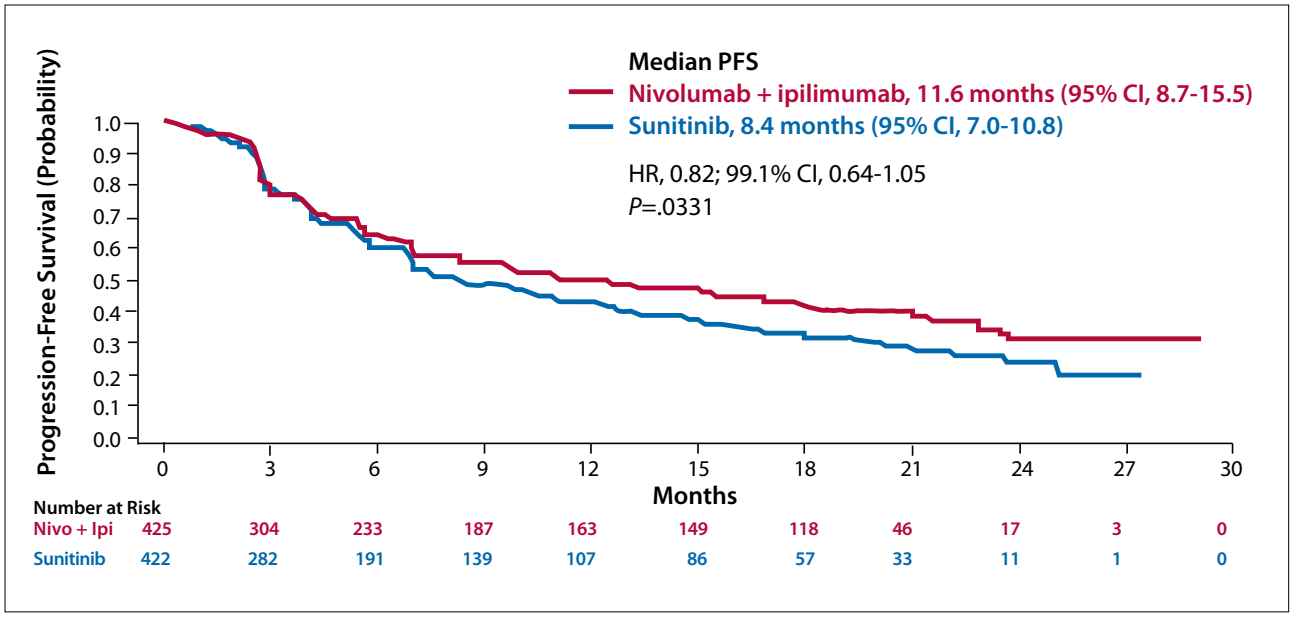

Figure 4. Progression-free survival for nivolumab plus ipilimumab vs sunitinib. HR, hazard ratio; Ipi, ipilimumab; Nivo, nivolumab. Adapted from Escudier B et al. ESMO abstract LBA5. *Ann Oncol.* 2017;28(suppl 5).[2]

patients with a PD-L1 expression of less than 1% who were at intermediate to poor risk, ORR was 37% (95% CI, 32%-43%) with nivolumab plus ipilimumab vs 28% (95% CI, 23%-34%; *P*=.0252) with sunitinib. In patients with a PD-L1 expression of at least 1% who were at intermediate to poor risk, ORR was 58% with combination treatment vs 22% with sunitinib (95% CI, 15%-31%; *P*<.0001). In the intent-to-treat patients with low PD-L1 expression, ORR was 36% (95% CI, 31%-41%) with nivolumab plus ipilimumab vs 35% (95% CI, 31%-40%) with sunitinib monotherapy (*P*=.8799). In the intent-to-treat patients with PD-L1 expression of at least 1%, the ORR was 53% (95% CI, 44%-63%) with combination therapy vs 22% (95% CI, 15%-30%) with sunitinib monotherapy (*P*<.0001). For all of these patient cohorts, combination treatment yielded a superior CR rate. In patients at intermediate to poor risk, median PFS was similar for both treatments in those with PD-L1 expression of less than 1% (11.0 months vs 10.4 months; *P*=.9670). However, median PFS was significantly better with combination treatment in patients with higher PD-L1 expression (22.8 months vs 5.9 months; *P*=.0003).

At the 2017 meeting of the Society for Immunotherapy of Cancer, data were presented for OS.[3] Nivolumab plus ipilimumab was superior to sunitinib, regardless of the patient's PD-L1 expression (<1%: HR, 0.73; 95% CI, 0.56-0.96 and ≥1%: HR, 0.45; 95% CI, 0.29-0.71). OS was not reached for nivolumab plus ipilimumab or sunitinib for patients with PD-L1 levels of less than 1%. For patients with PD-L1 levels of 1% or higher, the median OS was not reached for the combination vs 19.6 months for sunitinib.

As Dr Rini reported, grade 3/4 AEs were observed in 46% of patients in the combination treatment arm vs 63% of patients in the sunitinib monotherapy arm. The most common grade 3/4 AEs in the combination arm were fatigue (4%), diarrhea (4%), and nausea (2%) in the combination arm and hypertension (16%), fatigue (9%), and palmar-plantar erythrodysesthesia syndrome (9%) in the sunitinib arm. AEs leading to discontinuation occurred in 22% of patients in the combination arm vs 12% in the sunitinib arm.

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How Should We Treat Brain Metastases From Renal Cell Carcinoma?

Dr Bernard Escudier discussed treatment of brain metastases in patients with RCC.[1] Brain metastases develop in approximately 8% of RCC patients and are associated with a negative prognosis.[2-5] Local therapy is recommended when possible. Single metastases are more likely to be controlled than multiple metastases, and the risk of recurrence rises with increasing numbers of metastases, worsening symptoms, and larger size.[6] Stereotactic radiotherapy is effective, and tumor control can be achieved with a single dose of 24 Gy.[7] Although survival decreases with increasing numbers of brain lesions (Figure 5), as many as 10 brain metastases can be treated with stereotactic radiotherapy.[8] Local control becomes more challenging with increasing lesion size. Owing to increasing risk of relapse and radionecrosis, 3 cm is considered the largest size appropriate for treatment with stereotactic radiotherapy.[9-12]

Brain metastases are highly heterogeneous across tumor types. In patients with non–small cell lung cancer, PD-L1 expression levels are higher in brain metastases compared with the paired primary tumor.[13] The presence of a dense infiltration of effector cells is associated with an improved prognosis. However, in a study of brain metastases in patients with various primary tumor types, PD-L1 expression did not correlate with the density of tumor-infiltrating lymphocytes.[14] The density of tumor-infiltrating lymphocytes varied among primary tumor types, with the highest density observed in the brain metastases of patients with primary melanoma, followed by RCC and lung cancer. A high density of infiltration was most common in tumor-infiltrating lymphocytes that were CD3+ (82%) and least common in those that were PD1+ (15.5%; *P*<.001). The density of certain tumor-infiltrating lymphocytes positively correlated with improved median OS. The expression of PD-L1 and MET was further investigated in a large study of patients with metastatic RCC.[15] The study evaluated specimens from 42 primary tumors and 138 metastases, including 87 brain and 51 pancreatic metastases. The study found lower expression of PD-L1 and MET in the primary RCC tumor vs brain or pancreatic metastases, and expression of MET was significantly higher in brain metastases compared with pancreatic metastases.

Treatment with nivolumab monotherapy was evaluated in a prospective phase 2 study that included 55 patients with metastatic RCC and brain metastases.[16] The proportion of patients with 1, 2, or more than 2 brain metastases was 67%, 12%, and 21%, respectively. Two-thirds of patients had not received prior treatment for their brain metastases. Patients were treated with nivolumab (3 mg/kg) every 2 weeks. Objective responses were observed in 23% of patients, all of whom had received prior treatment for their brain metastases (consisting of either surgery or radiotherapy). Local

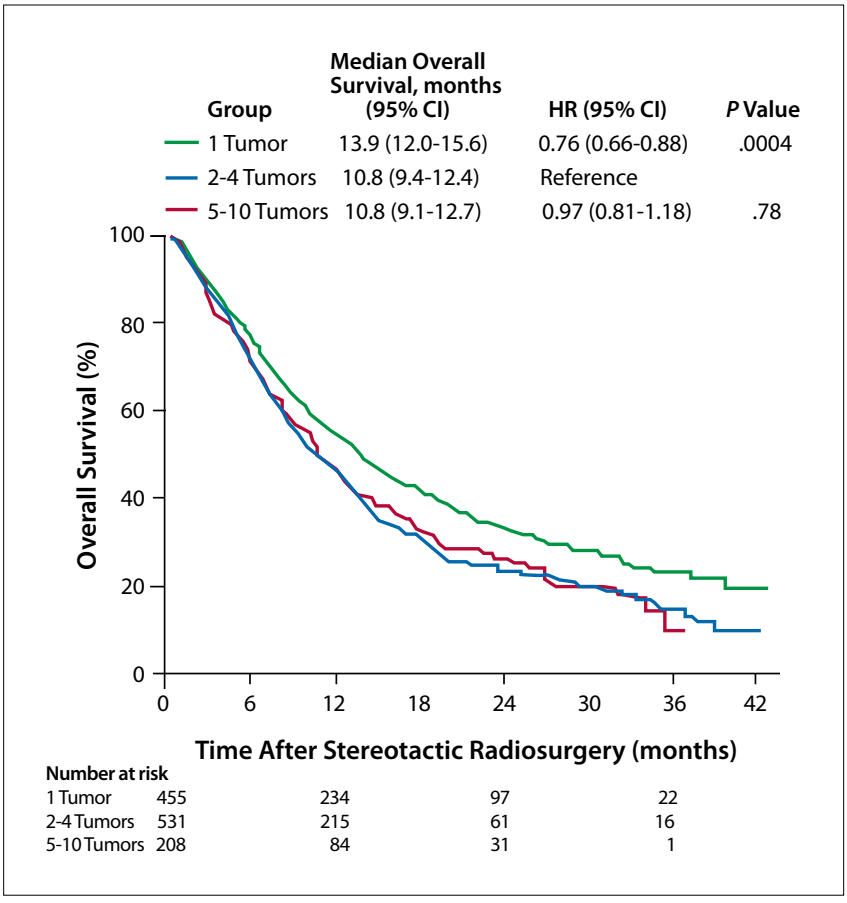

Figure 5. Survival according to the number of lesions in patients with brain metastases. HR, hazard ratio. Adapted from Yamamoto M et al. *Lancet Oncol.* 2014;15(4):387-395.[8]

ABSTRACT SUMMARY Sunitinib in Patients With High-Risk Renal Cell Carcinoma: Safety and Therapy Management in the S-TRAC Trial

Dr Bernard Escudier evaluated safety of adjuvant sunitinib and therapy management measures among patients in the S-TRAC study, which compared sunitinib vs placebo in patients with RCC. Among the 306 patients treated with sunitinib, 71% remained on treatment for at least 8 months, and 51% completed the full year of treatment. The median treatment duration was 12.4 months (range, 0.1-14.9 months), and the median relative dose intensity was 88.4% (range, 15.0%-106.2%). More than half of patients (55.6%) completed a year of treatment. Among sunitinib-treated patients, 45.8% had dose reductions, 41.5% had dose delays, and 54.2% had dose interruptions. In the sunitinib arm, AEs were the most frequent reason for dose reductions (34.6%) and dose interruptions (46.4%). The median time to discontinuation of sunitinib was 4.5 months. Palmar-plantar erythrodysesthesia syndrome was the most common AE reported as the reason for sunitinib discontinuation (4.2%), dose reduction (11.8%), and dose interruption (6.2%). However, most palmar-plantar erythrodysesthesia syndrome events were of grade 1 or 2, and fewer than 5% of patients permanently discontinued treatment because of the syndrome. AEs were generally manageable, predictable, and reversible by means of dose reduction or interruption or with standard supportive therapy.

tumor progression was reported in 48% of patients, and 32% experienced neurological deterioration requiring treatment with corticosteroids. Therefore, local therapy is recommended before initiation of therapy directed toward PD1/PD-L1.

The use of cabozantinib to treat brain metastases in patients with primary RCC is supported by the strong MET expression seen in these metastases, even if there is little or no expression in the primary tumor. Through the Italian expanded access program, 91 patients with metastatic RCC received treatment with cabozantinib.[17] Five of these patients had brain metastases. Cabozantinib (60 mg) was administered daily in 28-day cycles. Early data from these 5 patients suggested that cabozantinib treatment is feasible in this setting. In addition, isolated case studies suggest that cabozantinib may be active in reducing brain metastases in patients with RCC.

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Guidelines on Managing Small Renal Masses: Compare and Contrast

Dr Houston Thompson compared guidelines for the management of small renal masses.[1-5] For these tumors, the Canadian Urological Association recommends partial nephrectomy by open surgery or laparoscopy, or with robotic assistance.[2] Laparoscopic radical nephrectomy is reserved for tumors that are not suitable for partial nephrectomy. The Canadian guidelines state that open partial nephrectomy is preferred to laparoscopic radical nephrectomy. Ablation is also an option, although it is less successful in patients with endophytic central tumors. A biopsy should be obtained at the time of ablation. A laparoscopic approach is unnecessary. Active surveillance is a primary consideration for the elderly and infirm.

The European Association of Urology (EAU) guidelines also recommend partial nephrectomy and state that surgery is the only curative treatment supported by high-quality evidence.[3] Laparoscopic radical nephrectomy is recommended for renal masses that are not eligible for treatment with partial nephrectomy. Owing to a lack of high-quality studies, the EAU guidelines provide no recommendations on ablation. However, the guidelines state that ablation can be offered to patients with comorbidities, RCC syndromes, bilateral tumors, or solitary kidney tumors. Ablation is not recommended for larger tumors or those near the hilum or ureter. Similarly to the Canadian guidelines, the EAU guidelines state that active surveillance is an option for elderly patients and those with comorbidities.

Guidelines from the American Society of Clinical Oncology (ASCO), published in early 2017, state that active surveillance should be the initial approach in patients with a life expectancy of less than 5 years, or patients with a renal mass of less than 1 cm and a life expectancy of less than 10 years.[4] Active treatment should be considered if the mass grows more than 5 mm annually or if it exceeds 4 cm. Partial nephrectomy is standard for patients who need treatment. Ablation is an option when complete removal of the mass is possible, and a biopsy should be performed before or during the procedure. The guidelines contradict the historical notion that ablation is limited to patients who are infirm or who have comorbidities. Even at centers with expertise, radical nephrectomy should be reserved for cases in which partial nephrectomy is not an option and the tumor shows significant complexity.

Guidelines from the Australian Urology Association state that partial nephrectomy should be prioritized when intervention is indicated, and that most cT1b/T2 tumors are eligible for this procedure.[5] Radical nephrectomy is preferred if all of the following conditions are met: high tumor complexity, no chronic kidney disease or proteinuria, a normal contralateral kidney, and, after treatment, anticipation of a normal glomerular filtration rate exceeding 45 mL/min. Radical nephrectomy should be avoided for cT1a renal masses. Ablation is an option for tumors of less than 3 cm. A percutaneous technique is preferred, and the physician should counsel the patient on the increased risk of local recurrence. Active surveillance is an acceptable option, especially if the tumor is less than 2 cm. Intervention may be considered if there is more than 5 mm of growth annually (which is in agreement with the ASCO guidelines), or if the tumor is greater than 3 cm (vs >4 cm in the ASCO guidelines). Rates of local recurrence were evaluated for

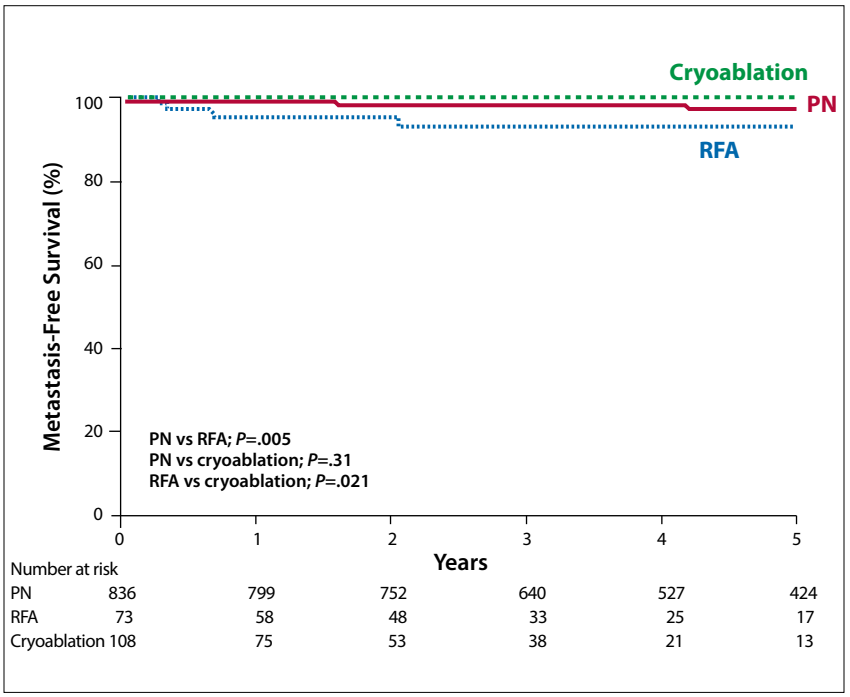

Figure 6. Metastasis-free survival among patients with cT1a renal cell carcinoma after PN, RFA, or cryoablation. PN, partial nephrectomy, RFA, radiofrequency ablation. Adapted from Thompson RH et al. *Eur Urol*. 2015;67(2):252-259.[6]

partial nephrectomy and percutaneous ablation for the treatment of cT1 renal masses.[6] The authors searched the prospectively maintained Mayo Clinic Renal Tumor Registry and identified 1803 patients with cT1N0M0 renal masses treated between 2000 and 2011. Rates of recurrence-free survival were similar among patients who underwent partial nephrectomy or percutaneous ablation. Among patients with a cT1a renal mass, metastases-free survival was superior with partial nephrectomy and cryoablation when compared with radiofrequency ablation (Figure 6).

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Imaging in Renal Cell Carcinoma: Novel Methods and Approaches

Dr Mark Ball presented insights on novel imaging methods in RCC.[1] RCC tumors have been shown to exhibit grade heterogeneity, with most small renal masses and high-grade tumors exhibiting nuclear-grade heterogeneity (Figure 7).[2] Imaging modalities, including computed tomography (CT), magnetic resonance imaging (MRI), and nuclear medicine may provide more detailed tumor information for use in classification and risk stratification.

Diffusion-weighted MRI has been evaluated for its ability to further characterize focal renal lesions.[3] The method provides contrast within tissues and is sensitive to cell density, membrane integrity, and tissue microstructure.[4] A retrospective study evaluated the apparent diffusion coefficient in the solid portions of RCC specimens, as well as in cystic or hemorrhagic areas, and in normal parenchyma in specimens from 33 patients with 36 RCC tumors.[3] Histologic subtype, nuclear grade, and cell count were also determined for each lesion. A decrease in the apparent diffusion coefficient was observed with increasing tumor grade, and the mean apparent diffusion coefficient of high-grade RCC tumors was significantly lower than in high-grade tumors (P=.005). Moreover, the mean apparent diffusion coefficient for clear cell RCC tumors was significantly higher than for non–clear cell tumors (P=.005).

This approach was further investigated in a study examining 152 lesions consisting of the following types: 97 clear cell RCCs, 29 papillary RCCs, and 26 oncocytomas.[5] Apparent diffusion coefficient maps were segmented for volumetric and pixel-based histogram analysis. The histopathology of surgical specimens was used as a reference standard for the diagnosis of various RCC subtypes. The apparent diffusion coefficient ranged from 258 mm^2/sec to 3407 mm^2/sec for papillary RCC tumors and from 246 mm^2/sec to 3686 mm^2/sec for clear cell RCC tumors. The best percentile showed 96% sensitivity and 84% specificity, reflecting the highest sensitivity and specificity among all of the features (with an area under the curve of 95.2).

Nuclear imaging is also being explored as a noninvasive method to characterize localized RCC tumors. An open-label, multicenter study evaluated positron emission tomography (PET)/CT with iodine-124 conjugated to girentuximab in patients with clear cell RCC masses that were scheduled for resection.[6] Girentuximab is a chimeric monoclonal antibody that binds to carbonic anhydrase, which is overexpressed in more than 90% of clear cell RCC tumors. Iodine I-124 girentuximab was administered intravenously 2 to 6 days before imaging. Imaging was performed by PET/CT and contrast-enhanced CT. The average sensitivity was 86.2% for PET/CT and 75.5% for contrast-enhanced CT (P=.023). The average specificity was 85.9% for PET/CT and 46.8% for contrast-enhanced CT (P=.005). The negative predictive value was 94.4%, the positive predictive value was 69.4%, and the accuracy was 86.2%. The study validated iodine I-124 girentuximab as a molecular imaging biomarker for the detection of clear cell RCC.

Benign oncocytoma and RCC can be differentiated through imaging with technetium-99m-methoxyisobutylisonitrile (99mTc-MIBI) single-photon emission CT (SPECT).[7] Three patients with oncocytoma and 3 with RCC underwent imaging with 99mTc-MIBI SPECT/CT. The 3 oncocytomas showed radiotracer uptake at levels near or exceeding that of the normal renal parenchyma, with ratios ranging from 0.85 to 1.78. In contrast, uptake levels for the 3 RCC tumors ranged from 0.21 to 0.31. In a separate study, 99mTc-sestamibi combined with SPECT/CT correctly identified 5

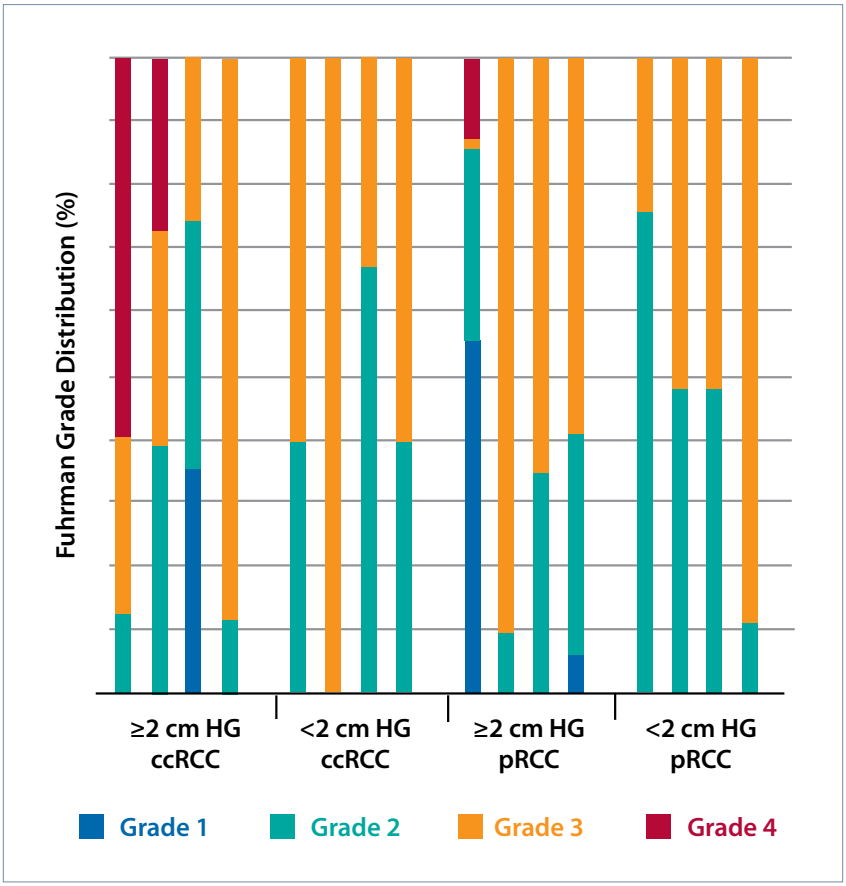

Figure 7. Grade heterogeneity of renal masses. CC, clear cell; HG, high-grade; p, papillary; RCC, renal cell carcinoma. Adapted from Ball MW et al. *J Urol.* 2015;193(1):36-40.[2]

of 6 oncocytomas and 2 of 2 hybrid oncocytic/chromophobe tumors.[8] The overall sensitivity was 87.5% (95% CI, 47.4%-99.7%), and specificity was 95.2% (95% CI, 83.8%-99.4%).

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A Perspective on Adjuvant Renal Cell Carcinoma Trials

Dr Tim Eisen discussed recent trials in RCC, with a focus on patient eligibility, endpoints, controversies across similar trials, and how to ensure that academic studies have regulatory impact in the context of adjuvant trials.[1] The currently available risk-scoring systems must be updated as new biomarkers and methods are developed. The SSIGN score (Stage, Size, Grade, and Necrosis) can be used to stratify patients based on the risk of metastasis-free survival.[2] Factors such as tumor stage, regional lymph node status, tumor size, nuclear grade, and histologic tumor necrosis were significantly associated with progression to metastasis in patients with clear cell RCC. Circulating tumor DNA (ctDNA) may provide a useful additional characteristic to monitor.[3-6] The half-life of ctDNA is very short; therefore, if complete resection of the tumor has been achieved, the ctDNA level should drop to 0 ng/mL soon after resection. ctDNA is most often monitored in patients with advanced disease who are receiving treatment. However, ctDNA could also find use in early diagnosis and screening. A study in stage II colorectal cancer demonstrated that ctDNA can be used to provide direct evidence of residual disease. Assays that incorporated massively parallel sequencing to detect ctDNA were used to investigate the ability to identify patients with minimal residual disease.[7] The study evaluated 1046 plasma samples from a prospective cohort of 230 patients with resected stage II colon cancer.[7] Among patients who did not receive adjuvant chemotherapy, ctDNA was detected postoperatively in 7.9%, and recurrence was observed in only 9.8% of patients with negative ctDNA (HR, 18; 95% CI, 7.9-40; $P<.001$). The presence of ctDNA in patients after completion of chemotherapy was also associated with an inferior recurrence-free survival (HR, 11; 95% CI, 1.8-68; $P=.001$). Other methods that should be considered for updating risk stratification include genetic signatures and imaging analyses.

Study endpoints are imperfect ways of measuring outcomes. OS is the

gold standard in any study of adjuvant therapy. However, use of OS as a study endpoint can lead to trials of excessive duration, and it can limit the number of questions that can be addressed. Disease-free survival and metastasis-free survival are acceptable endpoints in other settings, but there are doubts regarding their value as surrogate endpoints for survival. Quality-of-life and safety endpoints are important for assessing risk vs benefit, but the instruments available to measure them are not very accurate. These endpoints are unlikely to lead to new drug approvals.

Study data can be interpreted in different ways, leading to controversies. This situation is reflected in recent adjuvant trials in RCC, some of which are considered negative and others positive.[8] Similar questions are often asked across several different trials, and it might be more effective to design trials that are complementary instead of directly competing. In addition, enabling meta-analyses and incorporating patient-level data could prove fruitful. It is important for academic studies to have regulatory impact, but academic groups face major challenges in attracting industry support. It is expensive and difficult to prepare the regulatory quality data package. To increase the odds of successful regulatory review, data must be prepared in a format that suits submission requirements. Studies must be designed with central review of radiology, blinded evaluation by statisticians, on-site monitoring, periodic quality assessment, and use of electronic case report forms.

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Axitinib and Cabozantinib in the Treatment of Sunitinib-Refractory Patients With Metastatic Renal Cell Carcinoma: Results of Matching Adjusted Indirect Treatment Comparison Analysis of the AXIS and METEOR Trials

Dr Irina Proskorovsky presented results of matching-adjusted indirect treatment of comparison (MAIC) analysis of 2 trials that evaluated axitinib or cabozantinib in patients with metastatic RCC.[1] The phase 3 AXIS trial (Axitinib [AG 013736] As Second Line Therapy For Metastatic Renal Cell Cancer) evaluated axitinib vs sorafenib as second-line treatment in patients with metastatic RCC.[2] The open-label, phase 3 METEOR trial (A Phase 3, Randomized, Controlled Study of Cabozantinib [XL184] vs Everolimus in Subjects With Metastatic Renal Cell Carcinoma That Has Progressed After Prior VEGFR Tyrosine Kinase Inhibitor Therapy) compared cabozantinib vs everolimus in patients with metastatic RCC who developed progressive disease after treatment with a VEGF TKI.[3] Imbalances between studies preclude direct comparison of outcomes. MAIC analysis is a method for comparing results in similar trials by adjusting for imbalances in baseline patient characteristics.[4] MAIC analysis was performed to compare PFS and OS with axitinib vs cabozantinib in sunitinib-refractory patients enrolled in the AXIS and METEOR trials. The analysis was based on patient-level data from AXIS and published summary data from METEOR.

The comparison included 3 key steps. Baseline characteristics were mathematically adjusted so that the aggregate characteristics of the axitinib subgroup in AXIS matched those of the cabozantinib subgroup in METEOR. The adjustment factors derived in step 1 were then applied to generate the adjusted PFS and OS outcomes using a weighted Kaplan-Meier approach. Estimates of the comparative effect were quantified as an HR with a 95% CI. All available patient characteristics in both trials were used for adjustment, including risk classification based on criteria from the Memorial Sloan Kettering Cancer Center (MSKCC).[5] MSKCC risk was calculated differently in the 2 trials. The Karnofsky performance score (PS) was collected in METEOR, but not AXIS. The AXIS trial used criteria from the Eastern Cooperative Oncology Group (ECOG) to assess performance. The respective PS values in each trial were used to calculate the MSKCC risk classification. To evaluate the sensitivity of the results to the

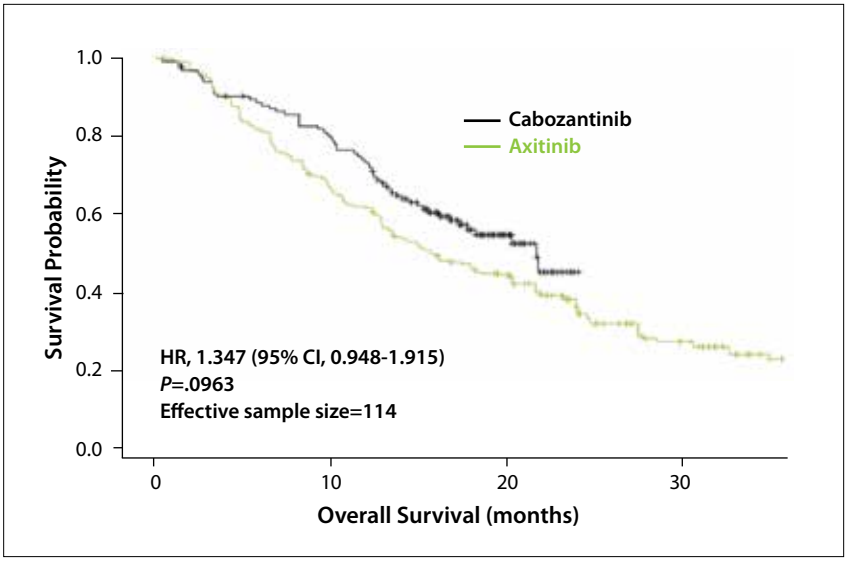

Figure 8. Sensitivity analysis of progression-free survival in a matching-adjusted indirect treatment comparison of data from trials evaluating axitinib and cabozantinib. HR, hazard ratio. Adapted from Proskorovsky I et al. Presented at: the Sixteenth International Kidney Cancer Symposium; November 3-4, 2017; Miami, Florida.[1]

ABSTRACT SUMMARY Deferred Systemic Therapy for Metastatic Renal Cell Carcinoma: Preliminary Prospective Experience

In some patients with slowly growing metastases, it may be preferable to delay systemic therapy, which is not curative. Dr Michael Harrison evaluated deferred systemic therapy in a prospective study of 501 patients with metastatic RCC. Systemic therapy was delayed for at least 91 days in 184 patients and was initiated by day 90 in 317 patients. According to a physician survey, the primary reason for delaying systemic therapy was that the patient was undergoing active surveillance (63%). Other reasons included administration of local therapy (17%) and poor prognosis (2%). Median follow-up from the time of enrollment was 10.5 months (interquartile range 25%-75%, 6-16 months). As of the data cutoff, 68.5% of the 184 patients had not received systemic therapy. In the delayed systemic therapy cohort, the time from initial diagnosis to the diagnosis of metastatic disease was less than 1 year in 49.7% of patients and 1 year or longer in 50.3% of patients. The Functional Assessment of Cancer Therapy was used to assess quality of life. Quality of life was superior among patients in whom systemic therapy was delayed, based on overall results and the specific categories of physical well-being, emotional well-being, and functional well-being.

MSKCC definition in AXIS, 2 sets of MAIC analyses were performed. ECOG PS 1 was considered a risk factor in the base case analysis, but not in the sensitivity analysis.

Before the MAIC adjustment, a higher proportion of patients in the AXIS subgroup had bone or lung metastasis compared with the METEOR subgroup. The proportion of patients with ECOG PS 1 and the distribution of MSKCC PS scores were also imbalanced in the initial study populations. Other characteristics that were matched for the MAIC comparison included the geographic location, prior nephrectomy, and prior radiotherapy. After these characteristics were matched, the patient characteristics were balanced between the sunitinib-refractory populations in both studies.

PFS and OS were analyzed by MAIC analysis. Base case analysis of PFS showed no significant differences between the sunitinib-refractory patients from AXIS vs METEOR (HR, 1.152; 95% CI, 0.815-1.626; *P*=.423). Sensitivity analysis was consistent with a marginally superior PFS for cabozantinib (HR, 1.387; 95% CI, 0.999-1.924; *P*=.0504; Figure 8). Base case analysis of OS also showed similar outcomes for axitinib vs cabozantinib (HR, 1.004; 95% CI, 0.689-1.463; *P*=.9830), as did sensitivity analysis (HR, 1.347; 95% CI, 0.948-1.925; *P*=.0963).

There were several limitations to the analysis, including the earlier timing of the PFS assessments in the AXIS trial, the inability to fully adjust for differences in the definitions of the MSKCC score between the 2 trials, and the availability of only a subset of patient characteristics for the sunitinib-refractory population in the METEOR trial.

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Nivolumab in the CheckMate 374, CheckMate 016, and CheckMate 025 Trials

Several posters presented findings from studies that evaluated nivolumab in various settings. The open-label, phase 3b/4 CheckMate 374 study evaluated nivolumab in 3 cohorts of patients with advanced or metastatic RCC: those with clear cell RCC, those with non–clear cell RCC, and those with brain metastases.[1] Treatment consisted of intravenous nivolumab (240 mg) every 2 weeks. The study included 98 patients with clear cell RCC, 43 patients with non–clear cell RCC, and 1 patient with brain metastases. Nearly all of the patients (99%) with clear cell RCC had received at least 1 prior systemic therapy for their advanced disease, whereas the majority of non–clear cell RCC patients (65%) were treatment-naive. After a median follow-up of 8.0 months, the primary reason for treatment discontinuation was disease progression. Discontinuations owing to nivolumab toxicity occurred in 9 patients (9%) with clear cell RCC and 2 patients (5%) with non–clear cell RCC. The median duration of exposure was 5.1 months for patients with clear cell RCC and 3.3 months for patients with non–clear cell RCC. Grade 3/4 immune-related AEs reported in the clear cell RCC cohort included hepatitis (3.1%), increased levels of alanine transaminase and aspartate transaminase (both 1.0%), increased blood bilirubin (1.0%), and hyperbilirubinemia (1.0%). No grade 3/4 immune-related AEs were reported in the non–clear cell patient cohort, and no grade 5 immune-related AEs occurred across the 3 cohorts.

CheckMate 016 is a multicenter, open-label, parallel-cohort, dose-escalation phase 1 study of nivolumab in combination with ipilimumab, sunitinib, or pazopanib in patients with advanced or metastatic RCC.[2] The study assigned 33 patients to nivolumab (2 mg/kg every 3 weeks) plus sunitinib (50 mg daily) and 20 to nivolumab (2 mg/kg every 3 weeks) plus pazopanib (800 mg daily). The proportion of patients who had received prior systemic therapy was 42.4% in the nivolumab plus sunitinib arm and 100% in the nivolumab plus pazopanib arm. In the nivolumab plus sunitinib arm, the median duration of therapy was 45.1 weeks for nivolumab and 28.0 weeks for sunitinib. In the nivolumab plus pazopanib arm, the median duration of treatment was 15.1 weeks for nivolumab and 13.9 weeks for pazopanib. Grade 3/4 treatment-related AEs were observed in 82% of patients in the nivolumab plus sunitinib arm and in 70% of patients treated with nivolumab plus pazopanib. The most common treatment-related AEs in both arms were fatigue, diarrhea, and hypertension. Immune-modulating medication was used by 55% to 60% of patients in both arms. Serious treatment-related AEs of any grade were reported in 42% of patients in the nivolumab/sunitinib arm and in 10% of patients in the nivolumab/pazopanib arm. For the sunitinib combination, the confirmed ORR was 54.5% (95% CI, 36.4%-71.9%), and the median PFS was 12.7 months. For the pazopanib combination, the confirmed ORR was 45.0% (95% CI, 23.1%-68.5%), and the median PFS was 7.2 months.

The combination of nivolumab plus ipilimumab at different doses was evaluated in the CheckMate 016 trial.[3] Patients with advanced or metastatic RCC received 4 cycles of treatment every 3 weeks consisting of intravenous nivolumab at 3 mg/kg plus ipilimumab at 1 mg/kg (arm N3I1), nivolumab at 1 mg/kg plus ipilimumab at 3 mg/kg (arm N1I3), or nivolumab at 3 mg/kg plus ipilimumab at 3 mg/kg (arm N3I3). Thereafter, patients received nivolumab (3 mg/kg) every 2 weeks until disease progression or unacceptable toxicity. Forty-seven patients were enrolled in each arm.

The high-dosage arm (nivolumab at 3 mg/kg plus ipilimumab at 3 mg/kg) was stopped early owing to dose-limiting toxicity.[4] Median follow-up was approximately 3 years in the other arms. Among patients treated with nivolumab at 3 mg/kg plus ipilimumab at 1 mg/kg (N3I1), 72.3% discontinued owing to disease progression and 12.8% discontinued owing to toxicity. Among patients who received nivolumab at 1 mg/kg plus ipilimumab at 3 mg/kg (N1I3), 46.8% discontinued owing to disease progression and 29.8% owing to toxicity.

In the N3I1 arm, grade 3/4 treatment-related AEs occurred in 42.6% of patients, grade 3/4 treatment-related AEs leading to discontinuation were reported in 6.4% of patients, serious grade 3/4 treatment-related AEs occurred in 19.1% of patients, and AEs requiring immune-modulating medication occurred in 31.9% of patients. In the N1I3 arm, these rates were 63.8%, 19.1%, 34.0%, and 48.9%, respectively. The confirmed ORR was 36.2% in the N3I1 arm (including CRs in 10.6%), and 40.4% in the N1I3 arm (including CRs in 2.1%). Median PFS was 7.0 months in the N3I1 arm and 9.4 months in the N1I3 arm (Figure 9). Median OS was not reached in either arm. The results supported further investigation of the N3I1 combination in the phase 3 CheckMate 214 study.[5]

The phase 3 CheckMate 025 study demonstrated superior OS and a higher ORR for nivolumab compared with everolimus after at least 14 months of follow-up.[6] After a minimum follow-up of approximately 38 months, results from CheckMate 025 continued to demonstrate a survival benefit over everolimus in previously treated patients with advanced or metastatic RCC.[7] The study assigned

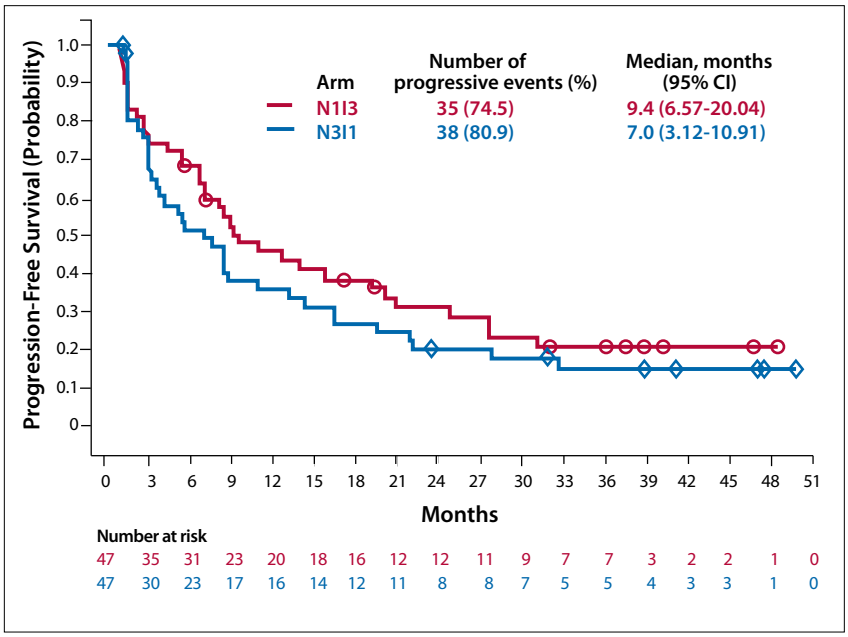

Figure 9. Progression-free survival in the CheckMate 016 trial. Patients in the N1I3 arm were treated with nivolumab at 1 mg/kg plus ipilimumab at 3 mg/kg. Patients in the N3I1 arm received nivolumab at 3 mg/kg plus ipilimumab at 1 mg/kg. Adapted from Plimack ER et al. Presented at: the Sixteenth International Kidney Cancer Symposium; November 3-4, 2017; Miami, Florida.[3]

406 patients to nivolumab (3 mg/kg every 2 weeks) and 397 to everolimus (10 mg daily). The median duration of treatment was 5.5 months (range, 5.1-6.9 months) with nivolumab and 3.7 months (range, 3.3-4.1 months) with everolimus. In both arms, the primary reason for discontinuation was disease progression (77% in the nivolumab arm and 74% in the everolimus arm). The median OS was 25.8 months with nivolumab vs 19.7 months with everolimus (HR, 0.74; *P*=.0005). Median PFS was 4.2 months with nivolumab vs 4.5 months with everolimus (HR, 0.85; *P*=.0371; Figure 10). The ORR was 26% with nivolumab vs 5% with everolimus.

Grade 3/4 treatment-related AEs occurred in 21% of patients treated with nivolumab and 37% of those treated with everolimus. Treatment-related AEs leading to discontinuation occurred in 5% vs 7%. The safety profile was consistent with the primary analysis, and the majority of AEs resolved.

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Highlights in Renal Cell Carcinoma From the Sixteenth International Kidney Cancer Symposium: Commentary

Robert A. Figlin, MD, FACP

Presentations at the Sixteenth International Kidney Cancer Symposium provided important insights into the evolving management of patients with renal cell carcinoma. Data were presented from new studies, subanalyses of pivotal trials, and retrospective analyses. Several of the abstracts were particularly noteworthy for the practicing clinician. The following discussion represents a perspective on the importance of these trial results as applied to the management of patients with renal cell carcinoma.

The CheckMate Trials

Dr Elizabeth Plimack presented an

updated analysis from the phase 1 CheckMate 016 trial (Checkpoint Pathway and Nivolumab Clinical Trial Evaluation 016).[1] CheckMate 016 evaluated nivolumab in combination with ipilimumab, sunitinib, or pazopanib in previously treated or treatment-naive patients with advanced or metastatic renal cell carcinoma.[2] The analysis by Dr Plimack focused on the cohort of patients treated with nivolumab plus ipilimumab, at 3 different dose levels. The results are potentially practice-changing, and they will likely be part of the submission package to the US Food and Drug Administration (FDA) for approval of combined immuno-oncology therapies in kidney cancer. Among the remarkable aspects of the study results is the tolerability of nivolumab plus ipilimumab. In addition, for the first time, a treatment has led to complete responses in addition to an overall response. With the regimen of nivolumab administered at 3 mg/kg plus ipilimumab at 1 mg/kg, the complete response rate exceeded 10%. (Complete responses are often associated with a significant improvement for patients with cancer.) The overall response rate was more than 35%, and the 12-month progression-free survival rate was 36%, which is impressive, especially in patients with refractory disease. Some of these responses were not only complete, but also durable. Treatment improved survival.

The phase 3 CheckMate 025 study compared nivolumab vs everolimus in patients with advanced kidney cancer.[3] Dr Padmanee Sharma presented an analysis of 3-year efficacy and safety.[4] Nivolumab is currently a standard-of-care treatment supported by level 1 evidence in patients with renal cell carcinoma previously treated with tyrosine kinase inhibitors (TKIs). This 3-year efficacy analysis aimed to determine whether responses to immuno-oncology agents are durable. The responses seen with nivolumab were remarkably durable, with a median overall survival of just under 26 months. On the Kaplan-Meier graph, there appears to be the potential for a tail to the curve at the 20% to 30% range, suggesting that these treatments may be associated with durable remissions that can be maintained. The optimal duration of nivolumab treatment is not known. The safety profile was favorable and consistent with the previously published primary data.[3] This analysis of the 3-year overall survival, efficacy, and safety further supports the use of immuno-oncology drugs, such as nivolumab, in the post-TKI population.

Not all combinations of immuno-oncology therapies are well-tolerated, as shown in an analysis of the phase 1 CheckMate 016 study presented by Dr Asim Amin.[5] This analysis focused on nivolumab in combination with either sunitinib or pazopanib. Targeted agents, such as the TKIs sunitinib or pazopanib, may prove to be less optimal for use in combination with immuno-oncology therapies. CheckMate 016 showed encouraging anti-tumor activity with an immuno-oncology therapy plus sunitinib or pazopanib, but these agents significantly increased the incidence of high-grade adverse events and dose-limiting toxicities. These combinations will not be evaluated further in the clinic or in pivotal phase 3 trials.

Ongoing phase 3 trials are combining targeted therapies with bevacizumab, cabozantinib, lenvatinib, and axitinib.[6-9] It is important to remember that not all combinations of immuno-oncology agents and targeted therapies are safe, and it will be necessary to wait for results from pivotal phase 3 trials to discern their importance and any potential differences among them.

Sunitinib

Dr Bernard Escudier presented a summary of the use of sunitinib, including safety and therapy management, among patients with resected high-risk localized renal cell carcinoma enrolled in the S-TRAC trial (A Clinical Trial Comparing Efficacy and Safety of Sunitinib Versus Placebo for the Treatment of Patients at High Risk of Recurrent Renal Cell Cancer).[10] In November 2017, the FDA approved sunitinib for the treatment of patients with high-risk resected renal cell carcinoma based on results from the S-TRAC trial.[11] This updated analysis demonstrated no new safety signals, and adverse events were similar to those previously reported with sunitinib in patients with advanced disease. The adverse events were predictable, manageable, and reversible. With effective therapy management, one could hope to achieve the prolonged disease-free survival benefit that has been seen in this population of patients treated with sunitinib. In fact, 71% of the patients were able to remain on treatment with sunitinib for at least 8 months, reaching cycle 6, and 56% of patients completed the entire year of treatment. This analysis further demonstrates that sunitinib is an option for the adjuvant treatment of kidney cancer in selected high-risk patients, as it is FDA-approved and associated with manageable, predictable side effects. Most patients can tolerate long-term treatment. A balanced discussion with patients in this subgroup is warranted.

Deferred Systemic Therapy for Metastatic Renal Cell Carcinoma

Dr Michael Harrison provided a preliminary prospective analysis evaluating deferred systemic therapy for metastatic renal cell carcinoma.[12] This issue is becoming increasingly important. The study by Dr Harrison builds on observations made in retrospective analyses by Dr Brian Rini and others suggesting that in some patients with kidney cancer, systemic therapy for advanced disease can be withheld until there is evidence of disease progression.[13,14] This strategy is known as active surveillance. The study by Dr Harrison prospectively enrolled more than 500 patients with

asymptomatic metastatic disease at 46 US sites, in both community and academic centers. At study entry, patients could be observed and followed without active therapy. Importantly, the results, although still preliminary, suggested that approximately one quarter of patients with advanced metastatic disease can be followed for up to nearly a year before they require systemic therapy. What does that mean for patients? For some asymptomatic patients with primarily lymph node– or lung-predominant disease who have previously undergone a nephrectomy, active surveillance is a reasonable alternative to treatment. These patients should undergo repeated computed tomography scans, and systemic therapy should be initiated when there is evidence of clinical progression. This prospective evaluation further demonstrates that an active surveillance approach may be appropriate for some patients.

Emerging Management Strategies

The year 2018 promises to be another important one in the evolution of kidney cancer care. On December 19, 2017, the FDA approved the use of cabozantinib in previously untreated metastatic patients. The approval was based on results from the CABOSUN study (Cabozantinib-S-Malate or Sunitinib Malate in Treating Patients With Previously Untreated Locally Advanced or Metastatic Kidney Cancer), which demonstrated superiority with cabozantinib compared with sunitinib.[15] We anxiously await the FDA's decision regarding the combination of ipilimumab/nivolumab in a similar population. After more than a decade of using TKIs within the initial treatment paradigm for advanced disease, we may be entering the era of upfront immuno-oncology approaches, based on the improvements seen in many endpoints, including survival. We also await the results of studies evaluating the combinations of checkpoint inhibitors combined with targeted agents, and the possibility that the ADAPT trial (Phase 3 Trial of Autologous Dendritic Cell Immunotherapy Plus Standard Treatment of Advanced Renal Cell Carcinoma) may provide information about the evolving role of vaccine therapy in this disease.[16]

Disclosure

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