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A SPECIAL MEETING REVIEW EDITION

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

A Review of Selected Presentations From the Seventeenth International Kidney Cancer Symposium • November 2-3, 2018 • Miami, Florida

Special Reporting on:

- CheckMate 214 Retrospective Analyses of Nivolumab Plus Ipilimumab or Sunitinib in IMDC Intermediate/Poor-Risk Patients With Previously Untreated Advanced Renal Cell Carcinoma With Sarcomatoid Features
- Phase Ib Study (COSMIC-021) of Cabozantinib in Combination With Atezolizumab: Results of the Dose-Escalation Stage in Patients With Treatment-Naive Advanced Renal Cell Carcinoma
- Second-Line VEGFR TKI Outcomes After First-Line Immune Checkpoint Blockade in Metastatic Renal Cell Carcinoma
- Rationally Targeting the Bone With Radium Plus Cabozantinib
- Phase II Trial of Intermittent Nivolumab in Patients With Metastatic Renal Cell Carcinoma Who Have Received Prior Anti-Angiogenic Therapy (NCT03126331)
- A Secreted PD-L1 Splice Variant That Covalently Dimerizes and Mediates Immunosuppression

PLUS Meeting Abstract Summaries

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NOW #1 TKI IN NEW PRESCRIPTIONS FOR aRCC[a]

[a]Based on IMS data as of October 2018, subject to change without notice.[1]

POWER FORWARD

WITH CABOMETYX® (cabozantinib)

CABOSUN was a randomized (1:1), open-label, multicenter trial of CABOMETYX vs sunitinib in 157 first-line patients with advanced RCC who had ≥1 IMDC risk factors.[2]

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.

CI=confidence interval; HR=hazard ratio; IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; IRRC=independent radiology review committee; PFS=progression-free survival; PPE=palmar-plantar erythrodysesthesia; RCC=renal cell carcinoma; TKI=tyrosine kinase inhibitor.

First and only TKI with superior efficacy to sunitinib in advanced RCC[2]

PRIMARY ENDPOINT: PFS*

8.6 months
CABOMETYX
(n=79)

vs

5.3 months
sunitinib
(n=78)

HR=0.48 (95% CI: 0.31-0.74), *P*<0.0008

52%
reduction in risk of progression or death

National Comprehensive Cancer Network® (NCCN®)

NCCN PREFERRED

Cabozantinib (CABOMETYX) is
THE ONLY NCCN "PREFERRED" TKI
for 1L intermediate/poor risk clear cell aRCC[3]

As defined by the the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®), preferred interventions are based on superior efficacy, safety, and evidence; and when appropriate, affordability

No new safety signals were observed with CABOMETYX in the CABOSUN trial[2]

- 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 retrospective blinded IRRC.

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. Data on file. Exelixis, Inc. IMS Health, October 2018. **2.** CABOMETYX® (cabozantinib) Prescribing Information. Exelixis, Inc, 2017. **3.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Kidney Cancer V.2.2019. ©National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed September 26, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

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

Learn more at CABOMETYXhcp.com

EXELIXIS®

CA-0994 11/18

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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CheckMate 214 Retrospective Analyses of Nivolumab Plus Ipilimumab or Sunitinib in IMDC Intermediate/Poor-Risk Patients With Previously Untreated Advanced Renal Cell Carcinoma With Sarcomatoid Features

Despite advances in the targeted treatment of renal cell carcinoma (RCC), the sarcomatoid subtype continues to present challenges.[1-3] Sarcomatoid dedifferentiation can occur in any RCC subtype or stage and is associated with resistance to established therapies. Most patients with sarcomatoid RCC have metastatic disease upon initial presentation, and the presence of sarcomatoid features independently predicts poor survival. Checkpoint inhibition may provide a desirable alternative to currently available treatments for this RCC subtype. Sarcomatoid RCC tumors may express programmed death 1 (PD-1) and its ligand (PD-L1) at higher rates than clear cell RCC tumors that lack sarcomatoid elements.[4] In a retrospective study, initial results based on inhibition of the immune checkpoint pathway showed promising efficacy in patients with metastatic RCC and sarcomatoid dedifferentiation.[5]

An exploratory analysis of the phase 3 CheckMate 214 study (Nivolumab Combined With Ipilimumab Versus Sunitinib in Previously Untreated Advanced or Metastatic Renal Cell Carcinoma) retrospectively evaluated the efficacy and safety of nivolumab plus ipilimumab vs sunitinib in patients with RCC with or without sarcomatoid features.[6] Included patients had treatment-naive, advanced or metastatic clear cell RCC, and intermediate- or poor-risk disease according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) model. Patients had a Karnofsky performance score of at least 70%, and tumor tissue available for PD-L1 testing.

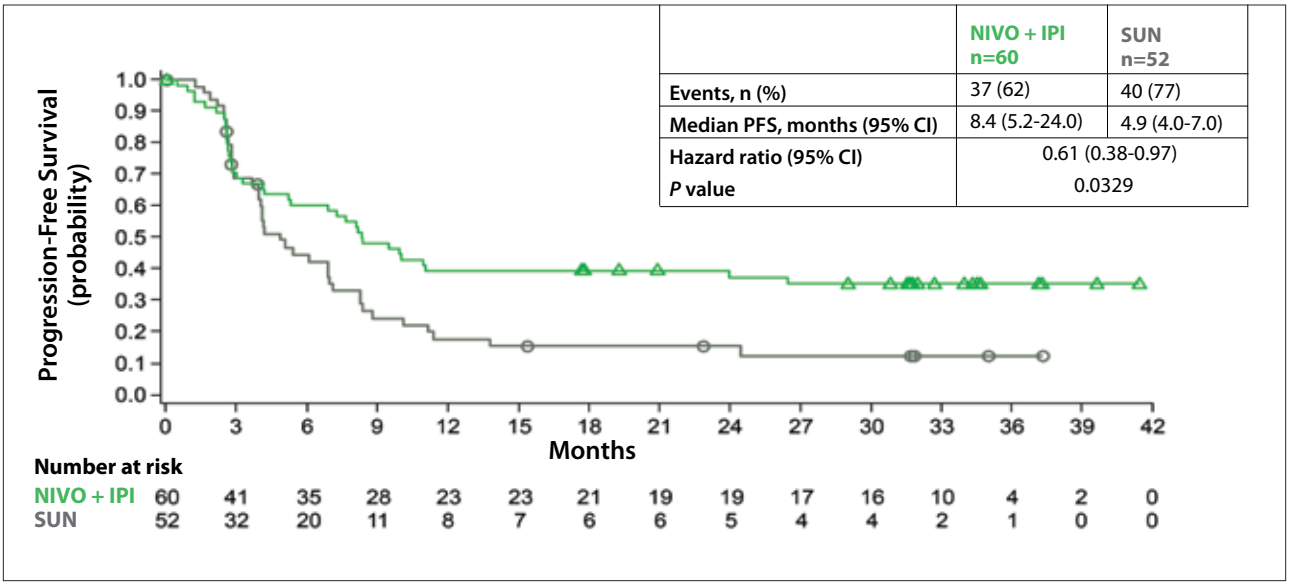
After stratification by IMDC prognostic score and region, patients were randomly assigned into the 2 treatment arms. Patients in arm A received nivolumab (3 mg/kg) plus ipilimumab (1 mg/kg) every 3 weeks for 4 cycles, followed by nivolumab (3 mg/kg) every 2 weeks. Patients in arm B received sunitinib (50 mg) once daily for 4 weeks on, 2 weeks off. Patients were treated until they developed disease progression or unacceptable toxicity.

The study randomly assigned 60 patients with sarcomatoid tumors to nivolumab plus ipilimumab (1 of whom was not treated) and 52 to sunitinib. The analysis also included 847 RCC patients with or without sarcomatoid features who were treated in CheckMate 214. In this comparator population, the study randomly assigned 425 patients to nivolumab plus ipilimumab and 422 to sunitinib.[7] Across the 4 arms, patients had a median age of 58 to 62 years, and 70% to 75% were male. A poor IMDC prognostic score was reported in 21% to 29%. The most common metastatic sites were the lung (69%-81%), lymph node (45%-51%), and bone (19%-23%). Among patients with available tissue, tumor PD-L1 expression of at least 1% was observed in 50% of those with sarcomatoid RCC vs 27.5% of those in the comparator population.

Among patients with sarcomatoid RCC, the confirmed objective response rate (ORR) was 56.7% (95% CI, 43.2%-69.4%) with nivolumab plus ipilimumab vs 19.2% (95% CI, 9.6%-32.5%) with sunitinib (P<.0001). In the comparator population of all patients randomly assigned to treatment, the ORR was 41.9% (95% CI, 37.1%-46.7%) vs 29.4% (95% CI, 25.1%-34.0%), respectively. The rate of complete response (CR) was 18.3% with nivolumab plus ipilimumab vs 0% with sunitinib. The median progression-free survival (PFS) was 8.4 months (95% CI, 5.2-24.0 months) in patients

ABSTRACT SUMMARY Safety and Efficacy of Checkpoint Inhibitors in Patients With Advanced Renal Cell Carcinoma and Pre-Existing Autoimmune Disorders

Dr Nieves Martinez Chanza presented results from a retrospective study of outcomes in advanced RCC patients with autoimmune disorders who received treatment with checkpoint inhibitors. Patients were treated at a single institution with a checkpoint inhibitor, either as monotherapy or in a combination regimen. Among 25 included patients, the most common autoimmune disorders were dermatologic (36%), rheumatologic (24%), or endocrine (24%). The ORR was 44% (95% CI, 24%-65%), including 1 CR. Two-year OS was 54% (95% CI, 31%-72%). Exacerbation of the autoimmune disorder was reported in 32% of patients; the most common events were arthritis, myalgia, rash, and eczema. New immune-related AEs affected 48% of patients. The majority of AEs were grade 1/2. Toxicities were generally manageable, but 3 patients permanently discontinued checkpoint inhibitor treatment.



	NIVO + IPI n=60	SUN n=52
Events, n (%)	37 (62)	40 (77)
Median PFS, months (95% CI)	8.4 (5.2-24.0)	4.9 (4.0-7.0)
Hazard ratio (95% CI)	0.61 (0.38-0.97)	
P value	0.0329	

Figure 1. Median progression-free survival (PFS) according to investigator assessment among intermediate- or poor-risk sarcomatoid patients treated with nivolumab plus ipilimumab (NIVO + IPI) vs sunitinib (SUN). Adapted from McDermott DF et al. CheckMate 214 retrospective analyses of nivolumab plus ipilimumab or sunitinib in IMDC intermediate/poor-risk patients with previously untreated advanced renal cell carcinoma with sarcomatoid features. Abstract presented at: the Seventeenth International Kidney Cancer Symposium; November 2-3, 2018; Miami, Florida.[6]

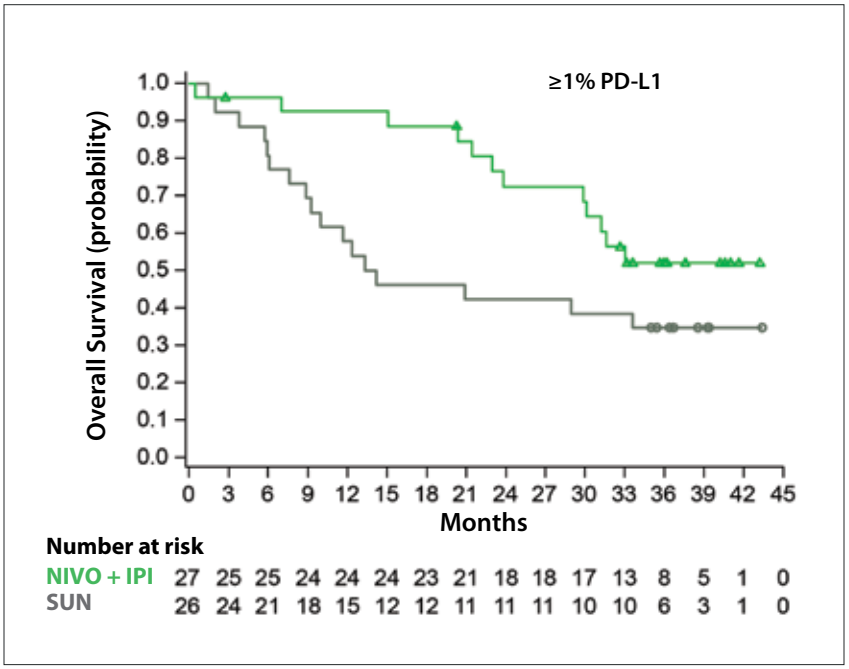


Figure 2. Median overall survival among intermediate- or poor-risk sarcomatoid patients with a programmed death ligand 1 expression level of 1% or higher treated with nivolumab plus ipilimumab (NIVO + IPI) vs sunitinib (SUN). Adapted from McDermott DF et al. CheckMate 214 retrospective analyses of nivolumab plus ipilimumab or sunitinib in IMDC intermediate/poor-risk patients with previously untreated advanced renal cell carcinoma with sarcomatoid features. Abstract presented at: the Seventeenth International Kidney Cancer Symposium; November 2-3, 2018; Miami, Florida.[6]

treated with nivolumab plus ipilimumab vs 4.9 months (95% CI, 4.0-7.0 months) in those who received sunitinib (hazard ratio [HR], 0.61; 95% CI, 0.38-0.97; *P*=.0329; Figure 1), based on investigator analysis. Median overall survival (OS) was 31.2 months (95% CI, 23.0 months to not reached) with nivolumab plus ipilimumab vs 13.6 months (95% CI, 7.7-20.9 months) with sunitinib (HR, 0.55; 95% CI, 0.33-0.90; *P*=.0155). OS was superior with nivolumab plus ipilimumab vs sunitinib regardless of the patient's level of PD-L1 expression. Among patients with less than 1% PD-L1 expression, the median OS was 23.7 months with nivolumab plus ipilimumab vs 13.8 months with sunitinib. Among patients with an expression level of 1% or higher, median OS was not reached vs 13.8 months, respectively (Figure 2). No new safety signals were raised for either treatment.

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Phase Ib Study (COSMIC-021) of Cabozantinib in Combination With Atezolizumab: Results of the Dose-Escalation Stage in Patients With Treatment-Naive Advanced Renal Cell Carcinoma

Cabozantinib is a tyrosine kinase inhibitor (TKI) that may act synergistically with immune checkpoint inhibitors.[1,2] The open-label phase 1b COSMIC-021 trial (Study of Cabozantinib in Combination With Atezolizumab to Subjects With Locally Advanced or Metastatic Solid Tumors) evaluated cabozantinib plus atezolizumab, a PD-L1 antibody, in patients with solid tumors.[3] The dose-escalation stage of the study used a 3 + 3 design. Enrolled patients had advanced or metastatic RCC or urothelial carcinoma. Patients with RCC were treatment-naive, and those with urothelial carcinoma had progressed on prior systemic platinum-based therapy. Patients had measurable disease and an Eastern Cooperative Oncology Group performance status of 0 or 1. All dose levels included atezolizumab (1200 mg, every 3 weeks). Cabozantinib was administered once daily at 20 mg (dose level –1), 40 mg (dose level 1), or 60 mg (dose level 2). Dose-limiting toxicities were evaluated during the first 21 days of treatment. Tumor assessment, using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, occurred every 6 weeks for the first 12 months and every 12 weeks thereafter.[4] The primary objective was to determine the maximum tolerated dose and the recommended dose of cabozantinib in combination with atezolizumab for the expansion phase of the study.

The study enrolled 10 patients with clear cell RCC and 2 with non–clear cell RCC at 3 sites in the United States. The median follow-up was 33 weeks (range, 26-50 weeks). All patients were receiving active treatment at the data cutoff point. Six patients entered into the dose level 1 cohort and 6 into the dose level 2 cohort. The patients' median age was 65.5 years (range, 49-77 years), and two-thirds were male. Both patients with non–clear cell RCC were enrolled in the lower dose cohort. IMDC risk status was favorable or intermediate in 11 patients. All patients had undergone prior nephrectomy. One patient enrolled in the lower dose cohort had received prior systemic therapy.

Based on investigator evaluation, the ORR was 50% (95% CI, 12%-88%) at dose level 1 and 83% (95% CI, 36%-100%) at dose level 2. One patient (8%) in the lower-dose cohort had a confirmed CR. A partial response (PR) was confirmed in 2 patients (33%) treated at dose level 1 and 5 patients (83%) at dose level 2. The remaining patients had stable disease, yielding a disease control rate of 100%. Among the 10 patients with clear cell RCC, the ORR was 80% and included 1 CR and 7 PRs. Among the 2 patients with non–clear cell RCC, 1 had progressive disease after approximately 30 weeks of study treatment and 1 had stable disease. The PD-L1 expression level was low for all 9 patients with available tumor tissue, and 6 of these patients had an objective response. The best sum of the target lesion change from baseline is shown in Figure 3. Time on treatment ranged from approximately 26 weeks to 50 weeks (Figure 4).

No dose-limiting toxicities, serious adverse events (AEs), or AEs of grade 4 or 5 were observed in either cohort. AEs requiring a dose reduction of cabozantinib occurred in 50% of patients treated at dose level 1 and in 100% of patients treated at dose level 2. AEs leading to dose interruptions occurred in 50% vs 67%, respectively. The dose of atezolizumab was interrupted owing to an AE in 17% at dose level 1 vs 67% at dose level 2. In the entire study population of 12 patients, the most common grade 3 AEs were hypertension (42%), hypophosphatemia (17%), and diarrhea (17%). Grade 3 immune-related AEs included increased levels of alanine, aspartate, or gamma-glutamyl transferase, increased lipase, and

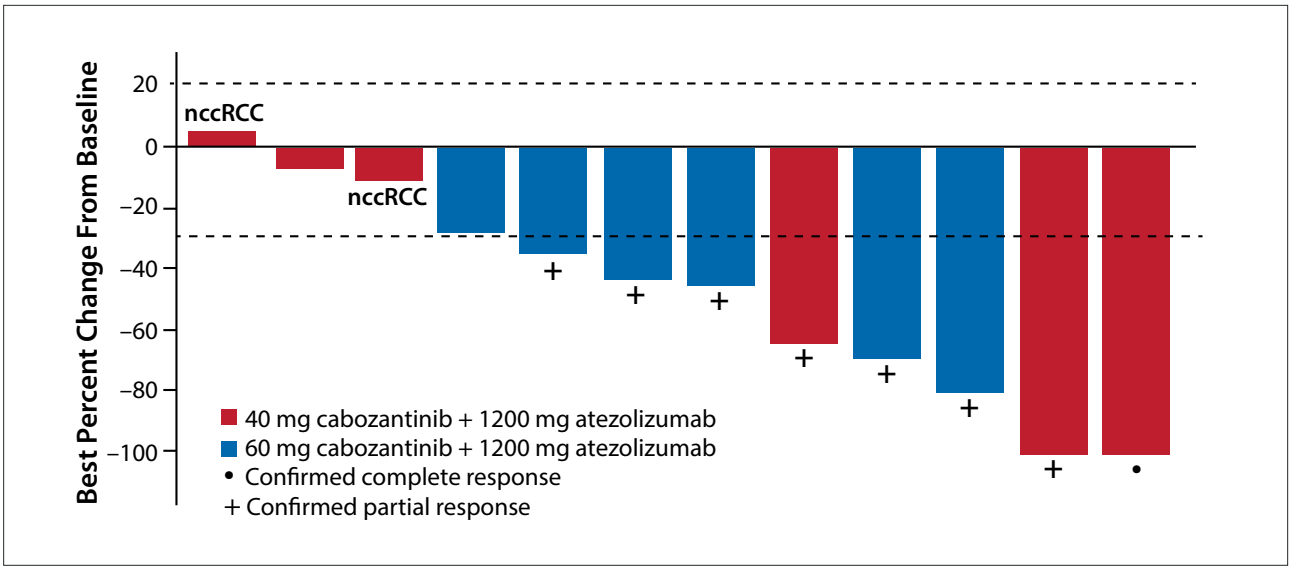

Figure 3. The best sum of target lesion change from baseline in a study of cabozantinib in combination with atezolizumab. nccRCC, non–clear cell renal cell carcinoma. Adapted from Agarwal N et al. Phase 1b study (COSMIC-021) of cabozantinib in combination with atezolizumab: results of the dose-escalation stage in patients with treatment-naive advanced renal cell carcinoma. Abstract presented at: the Seventeenth International Kidney Cancer Symposium; November 2-3, 2018; Miami, Florida.[3]

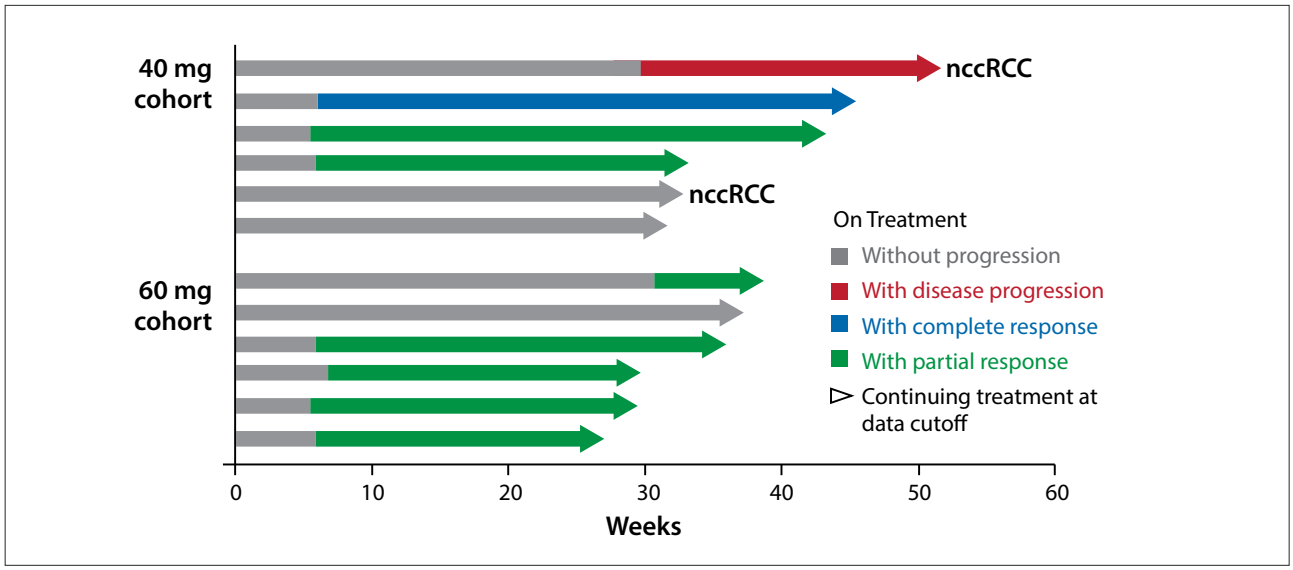

Figure 4. Time on treatment in a study of cabozantinib in combination with atezolizumab. nccRCC, non–clear cell renal cell carcinoma. The regimen consisted of cabozantinib at 40 mg or 60 mg plus atezolizumab at 1200 mg. Adapted from Agarwal N et al. Phase 1b study (COSMIC-021) of cabozantinib in combination with atezolizumab: results of the dose-escalation stage in patients with treatment-naive advanced renal cell carcinoma. Abstract presented at: the Seventeenth International Kidney Cancer Symposium; November 2-3, 2018; Miami, Florida.[3]

muscular weakness, each of which was observed in 1 patient (8%).

In summary, the combination of cabozantinib plus atezolizumab was well-tolerated and yielded a response in 8 of 10 patients with clear cell RCC. The recommended dose for the expansion phase was 40 mg daily for cabozantinib, with atezolizumab given at 1200 mg every 3 weeks. The expansion phase will evaluate the combined treatment in 12 tumor types, including RCC, urothelial carcinoma, and castration-resistant prostate cancer.

ABSTRACT SUMMARY Allogeneic Anti-CD70 CAR T Cells for Renal Cell Carcinoma

Dr Ewelina Morawa discussed clustered regularly interspaced short palindromic repeats (CRISPR)/caspase 9 gene editing, which is being applied to produce allogeneic anti-CD70 chimeric antigen receptor T cells (CTX130) for the treatment of solid and hematologic malignancies. CD70 is expressed in solid tumors and hematologic disorders, whereas expression in normal tissues is low. CD70 is highly expressed in RCC tumors. Potential advantages of allogeneic chimeric antigen receptor T-cell therapy over autologous therapy include immediate product availability and superior product consistency. By knocking out the relevant genes, CTX130 can be produced so that 99.5% of cells lack the T-cell receptor, thus reducing the likelihood of graft-vs-host disease. In a mouse model, growth of subcutaneous A498 RCC cells was halted in mice injected with CTX130, and multiplex gene editing has been demonstrated. A clinical study is planned to evaluate the efficacy and safety of CTX130 infusion.

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Second-Line VEGFR TKI Outcomes After First-Line Immune Checkpoint Blockade in Metastatic Renal Cell Carcinoma

Several drugs are now available for the treatment of advanced or metastatic RCC. These targeted therapies have diverse mechanisms of action, inhibiting the tyrosine kinase moiety on cellular receptors, the mammalian target of rapamycin, and members of the immune checkpoint pathway. With a large number of targeted therapies now available, treatment sequencing must be optimized to increase the CR rate and durability of responses, and to address the development of resistance to treatment.[1] A retrospective study evaluated the efficacy of second-line therapy with a TKI directed against the vascular endothelial growth factor receptor (VEGFR) after first-line therapy with an immune checkpoint inhibitor in patients with metastatic RCC.[2] The study included patients treated at 2 cancer centers and was based on chart review. IMDC risk was calculated based on the initiation of second-line VEGFR TKI therapy, and outcomes were based on blinded review according to RECIST 1.1.[3]

The study enrolled 70 patients. At diagnosis of metastatic RCC, their median age was 59 years (range, 43.6-74.8 years), and 71% were male. Stage IV disease was reported in 61% of patients. All of the patients had clear cell histology, and 20% had sarcomatoid dedifferentiation. At the time that the second-line treatment was initiated, the patients' IMDC risk score was favorable in 11%, intermediate in 69%, and poor in 20%. As first-line therapy, 17% of patients had received PD-1 monotherapy, 47% had received a PD-1 agent combined with CTLA-4 blockade, and 36% had received VEGF therapy combined with an inhibitor of PD-L1. The reasons for discontinuing first-line treatment included progressive disease in 83% and toxicity in 17%. The median duration of first-line treatment was 6.3 months (range, 0.48-27 months). The second-line treatment included axitinib (36%), cabozantinib (28%), pazopanib (27%), and sunitinib (9%).

Second-line treatment yielded an ORR of 41.2% and included 1 CR (1.5%; Figure 5). The disease control rate was 94.1%. The median PFS was 13.2 months (95% CI, 10.1 months to not reached), and 2-year PFS was 34.2%. The median OS was not reached (95% CI, 19.5 months to not reached), and 1-year OS was 79.6% (95% CI, 70.2%-90.3%).

The median duration of second-line therapy was 10.1 months (95% CI, 6.9-15.2 months). Thirty-three patients (47%) discontinued second-line treatment after developing progressive disease. Thirty-two patients (46%) required a dose reduction during second-line treatment. In 12 patients (27%), treatment with the VEGFR TKI was discontinued owing to AEs that included liver toxicity (7%), fatigue/anorexia (4%), aortic

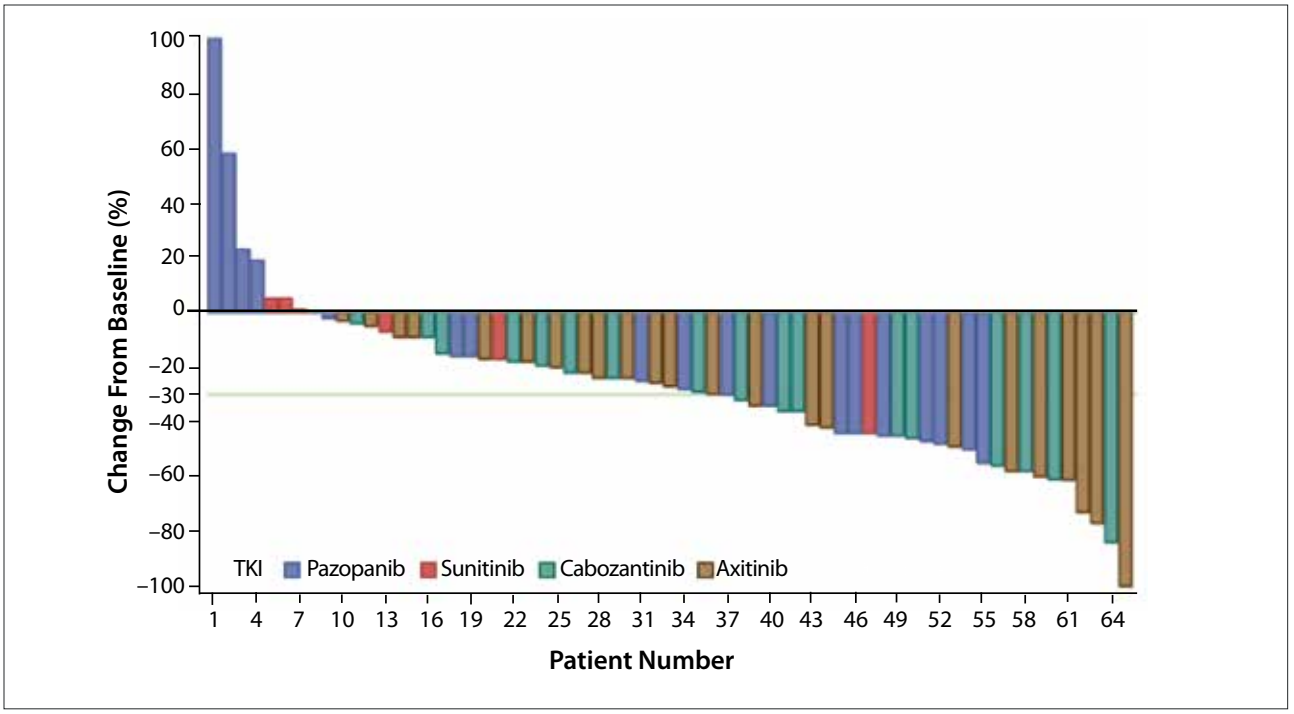

Figure 5. Overall response to a second-line VEGFR TKI after first-line immune checkpoint blockade. TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor. Adapted from Kotecha R et al. Second-line VEGFR TKI outcomes after first-line immune checkpoint blockade in metastatic renal cell carcinoma. Abstract presented at: the Seventeenth International Kidney Cancer Symposium; November 2-3, 2018; Miami, Florida.[2]

dissection (3%), palmar/plantar erythrodysesthesia (1%), and gastrointestinal bleeding (1%).

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Rationally Targeting the Bone With Radium Plus Cabozantinib

Bone metastases are frequently observed in patients with RCC and cause significant morbidity. In most patients, bone metastases lead to skeletal-related AEs, such as pain requiring radiation, pathologic fractures, spinal cord compression, and the need for surgery. Two large retrospective studies demonstrated an association between the presence of bone metastases and reduced survival.[1,2] Among 2749 patients with metastatic RCC in a clinical trials database, the median OS was significantly reduced in those with bone metastases (13.2 vs 20.1 months; HR, 0.774; *P*<.0001).[2] Both studies concluded that the presence of bone metastases was associated with reduced OS in all risk groups. In RCC patients, bone metastases result from dysregulation of markers of bone formation and resorption, affecting both osteoblasts and osteoclasts. Radium-223 dichloride is an alpha-emitting radiopharmaceutical that is a calcium mimetic.[3] As such, it selectively binds to areas of increased bone cell turnover and is incorporated into the bone stroma.

Radium-223 is approved by the US Food and Drug Administration for the treatment of patients with castration-resistant prostate cancer and bone metastases.[4] A pilot study evaluated radium-223 plus VEGFR-targeted therapy in patients with metastatic RCC of any histology and at least 1 bone metastasis that had not been treated with radiation.[5,6] The study

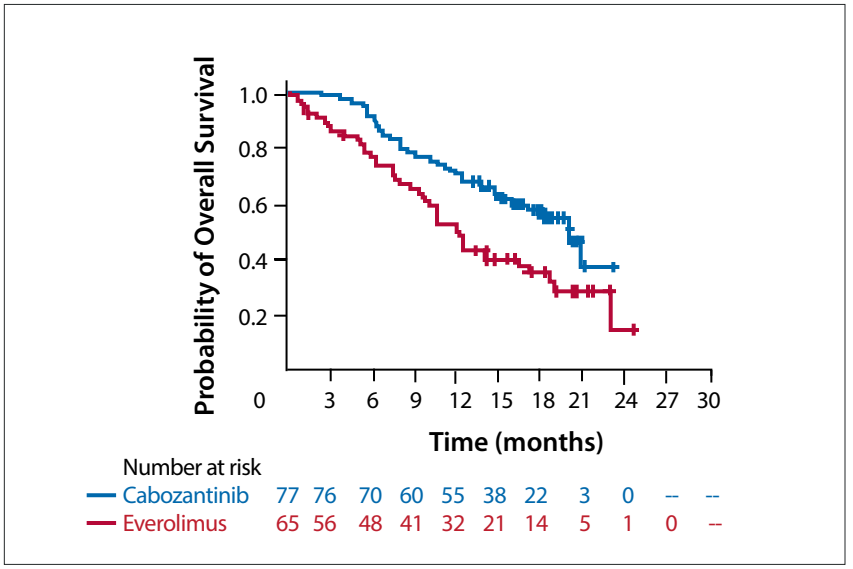

Figure 6. Probability of overall survival among patients with bone metastases treated with cabozantinib or everolimus. Adapted from Escudier B et al. *J Clin Oncol.* 2018;36(8):765-772.[9]

ABSTRACT SUMMARY Treatment-Free Survival Following Discontinuation of First-Line Nivolumab Plus Ipilimumab or Sunitinib in Patients With Advanced Renal Cell Carcinoma: CheckMate 214 Analysis

Dr Thomas Powles presented a post-hoc analysis of data from CheckMate 214 that evaluated treatment-free survival after discontinuation of therapy. Patients in this analysis had treatment-naive, advanced RCC, and their IMDC risk was intermediate or poor. Treatment with nivolumab plus ipilimumab delayed the time from randomization to second-line treatment by 6.7 months compared with sunitinib (15.2 vs 8.5 months; HR, 0.58; 95% CI, 0.49-0.68; *P*<.0001). Nivolumab plus ipilimumab also provided a benefit over sunitinib in patients who discontinued protocol therapy (treatment-free survival, 2.7 vs 1.4 months; HR, 0.55; 95% CI, 0.47-0.65; *P*<.0001), enabling many patients to delay or forego second-line treatment. Nivolumab plus ipilimumab was superior to sunitinib in patients with high or low baseline PD-L1 expression, those who achieved a CR or PR, and those with stable disease.

treated 15 treatment-naive patients with pazopanib and 15 previously treated patients with sorafenib. There was a safety run-in period for the first 6 patients in each cohort. Radium-223 (55 kBq/kg) was administered every 28 days for up to 6 infusions in both cohorts. Bone turnover markers were assessed at baseline, every 8 weeks, and off-treatment. The primary endpoint was the change in markers of bone turnover. In the entire study population, 77% of patients were male, and the median age was 62 years. Seventy percent of patients had clear cell histology, and 33% had liver metastases. A prior symptomatic skeletal event was reported in 83% of patients, 37% had received prior osteoclast-targeted therapy, and 84% had IMDC intermediate- or poor-risk disease.

The treatment combination was feasible and safe. Dose reductions were required in 1 patient in the pazopanib cohort and 4 patients in the sorafenib cohort. Patients received a median of 3 doses of radium-223. No dose-limiting toxicity was observed during the safety run-in. A treatment-related AE of grade 3/4 occurred in 44% of patients. Hematologic AEs were infrequent, with no grade 3/4 anemia, leukopenia, or thrombocytopenia in the pazopanib arm and 1 event (7%) of grade 3 anemia in the sorafenib arm.

All markers of bone formation and resorption showed dramatic declines at weeks 8 and 16 compared with baseline. N-terminal propeptide of type I procollagen showed the most dramatic change in expression level, from 45.5 µg/mL at baseline to a median maximum decline of –59.3 µg/mL. Other bone turnover markers, including C-terminal telopeptide, N-terminal telopeptide, bone-specific alkaline phosphatase, and osteocalcin showed maximum median declines of 29.2% to 50%.

The ORR was 23% with pazopanib plus radium-223 vs 9% with sorafenib plus radium-223. The median PFS was 8.2 months in the pazopanib cohort vs 3.6 months in the sorafenib cohort. Median OS was 16.6 months vs 14.2 months, respectively. Symptomatic skeletal events were observed in 47% of the pazopanib cohort vs 13% of the sorafenib cohort. By comparison, in the phase 3 COMPARZ trial (Pazopanib Versus Sunitinib in the Treatment of Locally Advanced and/or Metastatic Renal Cell Carcinoma), treatment with pazopanib in 557 patients with metastatic RCC yielded an ORR of 31%, a PFS of 8.4 months, and an OS of 28.4 months.[7] In both the current study and the COMPARZ trial, the Functional Assessment of Cancer Therapy—Kidney Symptom Index-19 questionnaire showed slightly worse outcomes while patients were receiving treatment.

Cabozantinib may be the superior TKI to combine with radium-223 in this setting (Figure 6).[8,9] In a subgroup analysis of the phase 3 METEOR trial

(A Study of Cabozantinib [XL184] vs Everolimus in Subjects With Metastatic Renal Cell Carcinoma), cabozantinib yielded a median PFS of 7.4 months in RCC patients with bone metastases.[9] The RADICAL trial will evaluate daily cabozantinib with or without radium-223 in patients with RCC of any histology and at least 2 untreated bone metastases. The trial will enroll patients who have received 2 or more prior lines of therapy and have current or prior symptoms related to bone metastases. Patients with impending spinal cord compression or pathologic fracture will be excluded. All patients will receive daily cabozantinib (40 mg to 60 mg). They will be randomly assigned to receive treatment with or without 6 cycles of radium-223 (55 kBq/kg every 28 days). The primary endpoint is symptomatic skeletal event–free survival. Enrollment of 132 patients is anticipated to provide an 84% power to detect a 42% reduction in the HR for symptomatic skeletal-related events.

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Phase II Trial of Intermittent Nivolumab in Patients With Metastatic Renal Cell Carcinoma Who Have Received Prior Anti-Angiogenic Therapy (NCT03126331)

Nivolumab is an approved treatment for patients with metastatic RCC who have received prior antiangiogenic therapy. The optimal duration of therapy, however, has not been confirmed. Recent studies suggest that some cancer treatments may provide a benefit even after treatment discontinuation. In a retrospective analysis of patients with advanced RCC in the phase 3 CheckMate 214 trial, patients in the nivolumab plus ipilimumab arm who discontinued treatment had a significantly prolonged treatment-free interval compared with those who discontinued in the sorafenib arm (P<.0001).[1] In a prospective phase 2 study of patients with treatment-naive, clear cell, metastatic RCC, treatment breaks from sunitinib did not appear to reduce clinical efficacy.[2]

A phase 2 trial evaluated intermittent nivolumab in patients with metastatic RCC who had received prior antiangiogenic therapy.[3,4] Treatment consisted of nivolumab (240 mg every 2 weeks or 480 mg every 4 weeks) administered for 12 weeks. Patients with a tumor burden decrease of less than 10% continued with standard therapy. Patients with a 10% or higher decrease in tumor burden stopped treatment for 12 weeks. After the treatment interruption, patients with a tumor burden increase of 10% or more resumed therapy until disease progression or a reduction in tumor

ABSTRACT SUMMARY Ipilimumab Plus Nivolumab as Salvage Therapy in Patients With Checkpoint Inhibitor–Refractory Metastatic Renal Cell Carcinoma

Dr Kimberly Allman presented results from a retrospective study evaluating outcomes in RCC patients who received nivolumab plus ipilimumab as second-line therapy. Among the 14 patients in the study, 7 had received prior nivolumab monotherapy. All had received prior therapy with a checkpoint inhibitor, with a median treatment duration of 11.2 months (range, 1-35 months). The best responses on prior checkpoint therapy included a CR in 1 patient (7%), a PR in 4 (29%), stable disease in 6 (43%), and progressive disease in 3 (21%). Patients received between 1 and 4 induction doses of nivolumab plus ipilimumab as second-line treatment. Among 12 patients, 4 (33%) had a PR, 3 (25%) had stable disease, and 5 (42%) had progressive disease. The median time on therapy was 3.6 months (range, 1 to 6+ months), and 7 patients (50%) remained on therapy at the time the study was reported. One grade 3 AE, thrombocytopenia, was noted. No toxicities occurred in 64% of patients.

Table 1. Outcome in a Phase 2 Trial of Intermittent Nivolumab in Patients With Metastatic Renal Cell Carcinoma Previously Treated With Anti-Angiogenic Therapy

Characteristic	n (%)
Best response	
Partial response	4 (29)
Stable disease	6 (43)
Progressive disease	4 (29)
Patients eligible for the intermittent phase	5 (36)
Patients agreeing to enter the intermittent phase	5 (100)
Treatment until eligibility for the intermittent phase	
12 weeks	4 (80)
24 weeks	1 (20)
Patients still in the intermittent phase	4 (80)

Data from Ornstein MC et al. Phase II trial of intermittent nivolumab in patients with metastatic renal cell carcinoma who have received prior anti-angiogenic therapy. Abstract presented at: the Seventeenth International Kidney Cancer Symposium; November 2-3, 2018; Miami, Florida.[3]

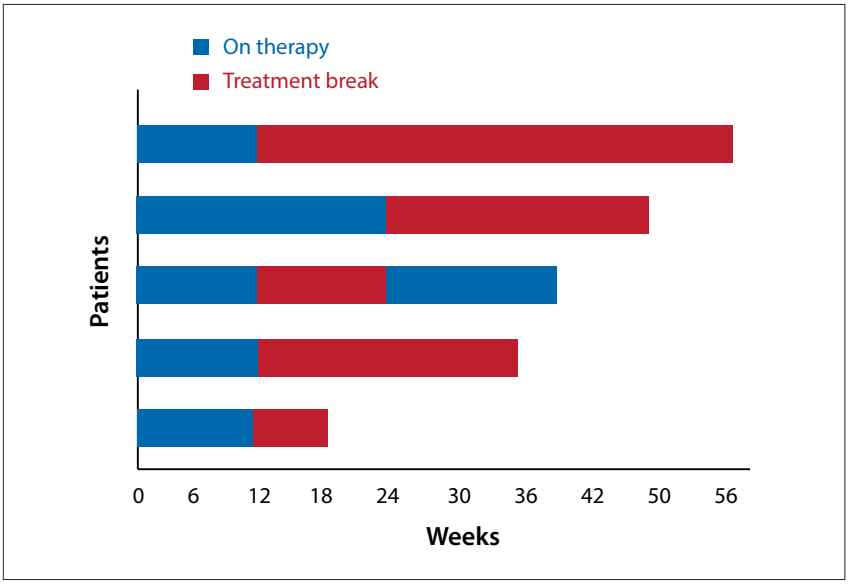

Figure 7. Response among patients who entered the intermittent phase in a trial of nivolumab in metastatic renal cell carcinoma treated with prior anti-angiogenic therapy. Adapted from Ornstein MC et al. Phase II trial of intermittent nivolumab in patients with metastatic renal cell carcinoma who have received prior anti-angiogenic therapy. Abstract presented at: the Seventeenth International Kidney Cancer Symposium; November 2-3, 2018; Miami, Florida.[3]

burden of at least 10%. Treatment was withheld in patients whose tumor burden did not increase by 10% or more. The study's primary objective was to determine the feasibility of intermittent nivolumab in patients with metastatic RCC.

Enrolled patients had histologic confirmation of RCC of any histology and advanced or metastatic disease as defined by RECIST 1.1.[5] Patients had received 3 or fewer prior treatments for advanced or metastatic RCC, and had a Karnofsky performance status of at least 70%. The trial accrued 14 patients from September 2017 through June 2018. The cohort was closed to further accrual after the approval of nivolumab plus ipilimumab as first-line treatment for metastatic RCC. Among the 14 enrolled patients, 93% were male, and the median age was 65 years (range, 57-72 years). Most patients (93%) had clear cell RCC histology, and 64% had an Eastern Cooperative Oncology Group performance status of 0. IMDC risk was favorable in 7%, intermediate in 86%, and poor in 7%. Metastatic sites included the lymph nodes (57%), bone (57%), lung (50%), and liver (21%). Eighty-six percent of patients had received 1 prior therapy, and sunitinib was the most recent therapy in 57% of patients.

After a median follow-up of 24.1 weeks (range, 4-57.4 weeks), the best responses were PR (29%), stable disease (43%), and progressive disease (29%; Table 1). Five patients (36%) were eligible for the intermittent phase. Four patients were eligible for the intermittent phase after 12 weeks, and 1 patient was eligible after 24 weeks of treatment with nivolumab. The median treatment-free interval was 24 weeks (range, 6-45 weeks; Figure 7). A new cohort will be enrolled to evaluate intermittent therapy and reinduction with ipilimumab plus nivolumab as first-line treatment in patients with metastatic RCC.

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A Secreted PD-L1 Splice Variant That Covalently Dimerizes and Mediates Immunosuppression

PD-L1 expression on RCC tumors is associated with a poor prognosis.[1] In a phase 3 pivotal trial of patients with previously treated advanced RCC, PD-1 blockade with nivolumab yielded a median OS of 27.4 months in those with PD-L1 expression of less than 1% vs 21.8 months in those with expression of 1% or higher.[2] Soluble PD-L1 has been identified as a potential prognostic biomarker that may be associated with outcomes for certain patients receiving treatment with checkpoint inhibitors.[3] Compared with serum from healthy donors, serum from stage IV melanoma patients prior to treatment showed increased levels of soluble PD-L1.

secPD-L1 is a splice variant of soluble PD-L1 with a unique 3' end. It also has 18 amino acids that are unique to this variant, including a cysteine residue that may allow it to dimerize. Dr Kathleen Mahoney presented results of in vitro studies that were performed to characterize secPD-L1.[4] Overexpression of secPD-L1 in the 300-19 leukemia cell line yielded dimers and higher multimers in the size range of 65 kD to 130 kD. Treatment with ß-mercaptoethanol showed a protein of approximately 40 kD, which was similar in size to the extracellular domain of PD-L1. Site-directed mutagenesis was used to replace cysteine-239 with a serine residue, and this eliminated the secPD-L1 multimers. An in vitro assay showed that secPD-L1 inhibited T-cell proliferation and production of γ-interferon in a dose-dependent manner. The unique 3' end of secPD-L1 was used for quantitative polymerase chain reaction and sequencing analyses. A positive correlation was observed between expression of full-length PD-L1 and secPD-L1 in cancer cell lines (Figure 8). A search of The Cancer Genome Atlas database showed that most tumors expressed both full-length PD-L1 and secPD-L1. In contrast, the majority of normal tissues expressed full-length PD-L1 but did not express secPD-L1. By gene set enrichment analysis, tumors that expressed secPD-L1 were found to express high levels of γ-interferon and S100A8. Expression of genes associated with myeloid-derived suppressor cells was also associated with expression of secPD-L1.

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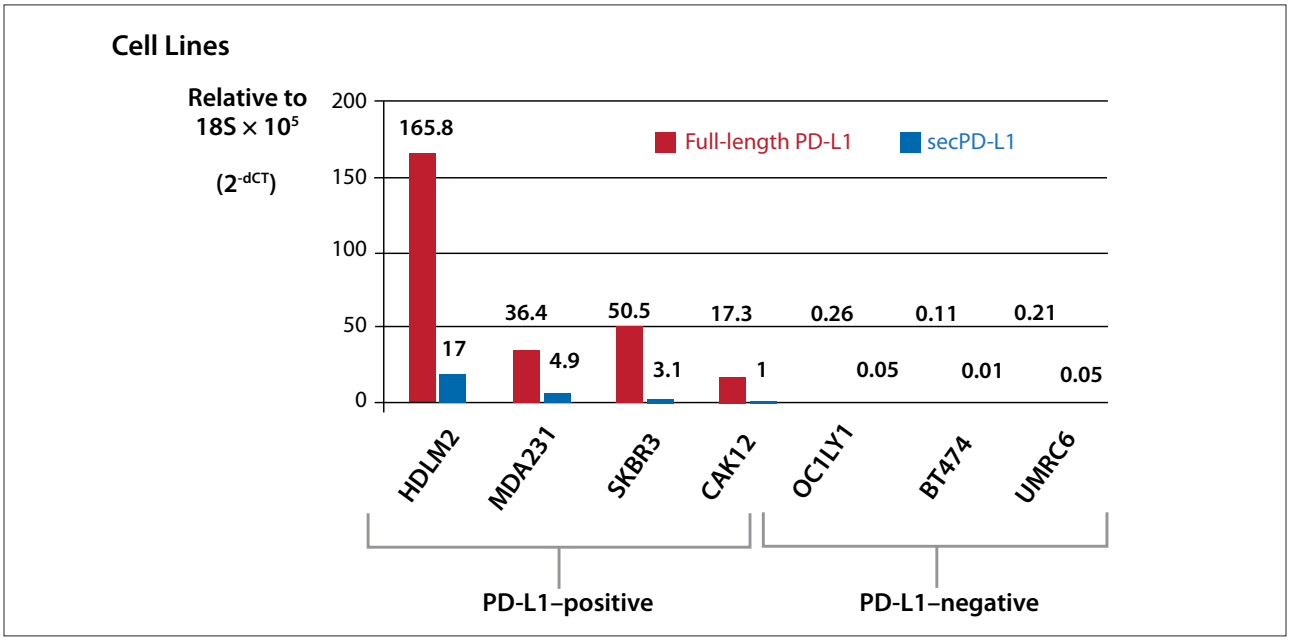

Figure 8. In an in vitro study, a positive correlation was observed between expression of full-length PD-L1 and secPD-L1 in cancer cell lines. secPD-L1 is a splice variant of soluble PD-L1 with a unique 3' end. PD-L1, programmed death ligand 1. Adapted from Mahoney K. A secreted PD-L1 splice variant that covalently dimerizes and mediates immunosuppression. Abstract presented at: the Seventeenth International Kidney Cancer Symposium; November 2-3, 2018; Miami, Florida.[4]


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