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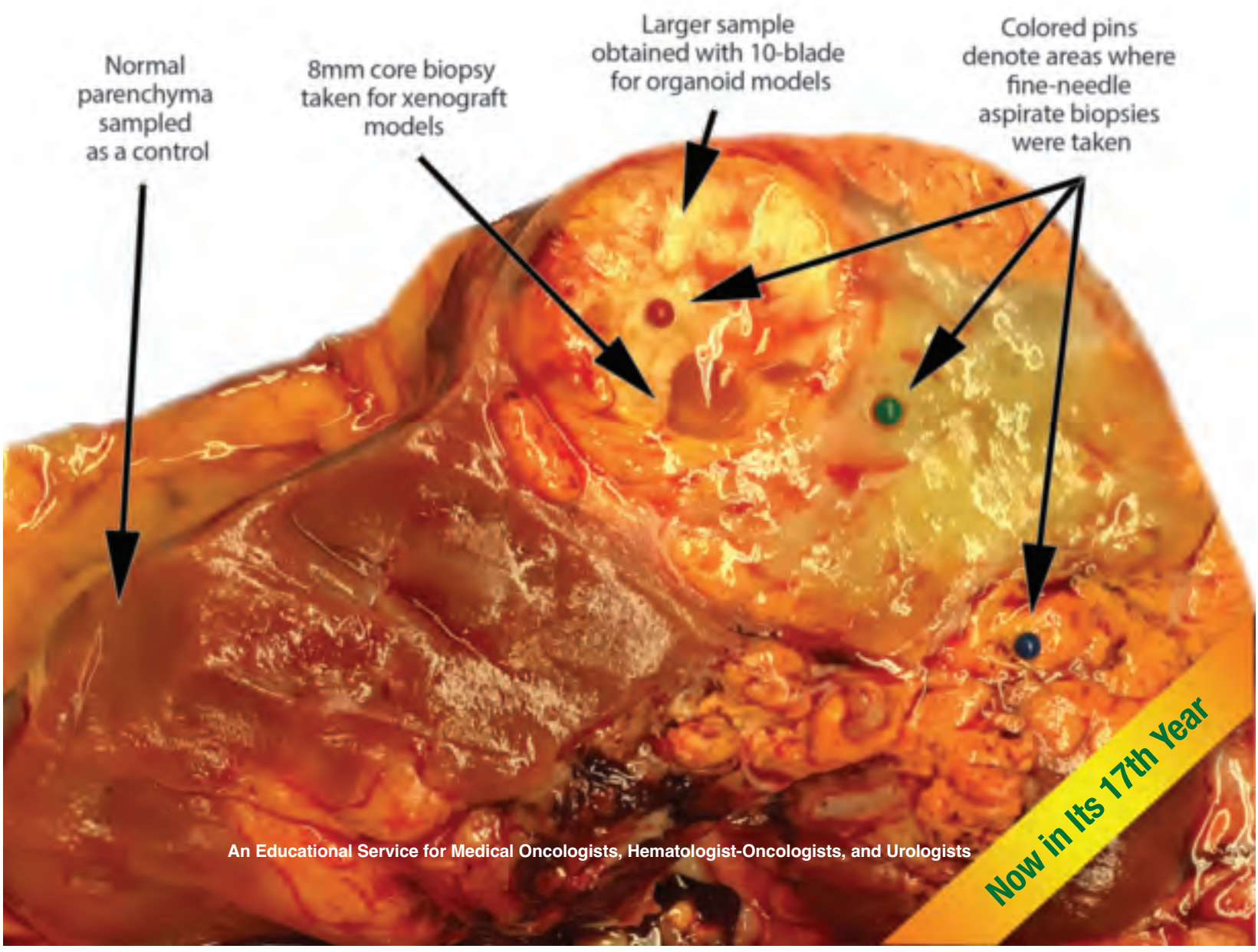

An Educational Service for Medical Oncologists, Hematologist-Oncologists, and Urologists

Now in Its 17th Year

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 THE **FIRST AND ONLY TKI** WITH **SUPERIOR EFFICACY** TO SUNITINIB[2]

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]

FIRST- AND SECOND-LINE aRCC

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 occurred with CABOMETYX. The incidence of Grade 3 to 5 hemorrhagic events was 5% in CABOMETYX patients. Discontinue CABOMETYX for Grade 3 or 4 hemorrhage. Do not administer CABOMETYX to patients who have a recent history of hemorrhage, including hemoptysis, hematemesis, or melena.

Perforations and Fistulas: Gastrointestinal (GI) perforations, including fatal cases, occurred in 1% of CABOMETYX patients. Fistulas, including fatal cases, occurred in 1% of CABOMETYX patients. Monitor patients for signs and symptoms of perforations and fistulas, including abscess and sepsis. Discontinue CABOMETYX in patients who experience a fistula that cannot be appropriately managed or a GI perforation.

Thrombotic Events: CABOMETYX increased the risk of thrombotic events. Venous thromboembolism occurred in 7% (including 4% pulmonary embolism) and arterial thromboembolism in 2% of CABOMETYX patients. Fatal thrombotic events occurred in CABOMETYX patients. Discontinue CABOMETYX in patients who develop an acute myocardial infarction or serious arterial or venous thromboembolic event requiring medical intervention.

Hypertension and Hypertensive Crisis: CABOMETYX can cause hypertension, including hypertensive crisis. Hypertension occurred in 36% (17% Grade 3 and <1% Grade 4) of CABOMETYX patients. Do not initiate CABOMETYX in patients with uncontrolled hypertension. Monitor blood pressure regularly during CABOMETYX treatment. Withhold CABOMETYX for hypertension that is not adequately controlled with medical management; when controlled, resume at a reduced dose. Discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis.

Diarrhea: Diarrhea occurred in 63% of CABOMETYX patients. Grade 3 diarrhea occurred in 11% of CABOMETYX patients. Withhold CABOMETYX until improvement to Grade 1 and resume at a reduced dose for intolerable Grade 2 diarrhea, Grade 3 diarrhea that cannot be managed with standard antidiarrheal treatments, or Grade 4 diarrhea.

Palmar-Plantar Erythrodysesthesia (PPE): PPE occurred in 44% of CABOMETYX patients. Grade 3 PPE occurred in 13% of CABOMETYX patients. Withhold CABOMETYX until improvement to Grade 1 and resume at a reduced dose for intolerable Grade 2 PPE or Grade 3 PPE.

Proteinuria: Proteinuria occurred in 7% of CABOMETYX patients. Monitor urine protein regularly during CABOMETYX treatment. Discontinue CABOMETYX in patients who develop nephrotic syndrome.

Osteonecrosis of the Jaw (ONJ): ONJ occurred in <1% of CABOMETYX patients. ONJ can manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration or erosion, persistent jaw pain, or slow healing of the mouth or jaw after dental surgery. Perform an oral examination prior to CABOMETYX initiation and periodically during treatment. Advise patients regarding good oral hygiene practices. Withhold CABOMETYX for at least 28 days prior to scheduled dental surgery or invasive dental procedures. Withhold CABOMETYX for development of ONJ until complete resolution.

Wound Complications: Wound complications were reported with CABOMETYX. Stop CABOMETYX at least 28 days prior to scheduled surgery. Resume CABOMETYX after surgery based on clinical judgment of adequate wound healing. Withhold CABOMETYX in patients with dehiscence or wound healing complications requiring medical intervention.

EXELIXIS®

CA-1000 01/19

CABOMETYX demonstrated a statistically significant improvement in median PFS vs sunitinib[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 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 for CABOMETYX were: diarrhea, fatigue, decreased appetite, PPE, nausea, hypertension, and vomiting

Reversible Posterior Leukoencephalopathy Syndrome (RPLS): RPLS, a syndrome of subcortical vasogenic edema diagnosed by characteristic finding on MRI, can occur with CABOMETYX. 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 and females of reproductive potential of the potential risk to a fetus. Verify the pregnancy status of females of reproductive potential prior to initiating CABOMETYX and advise them to use effective contraception during treatment and for 4 months after the last dose.

ADVERSE REACTIONS

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

DRUG INTERACTIONS

Strong CYP3A4 Inhibitors: If coadministration with strong CYP3A4 inhibitors cannot be avoided, reduce the CABOMETYX dosage. Avoid grapefruit or grapefruit juice.

Strong CYP3A4 Inducers: If coadministration with strong CYP3A4 inducers cannot be avoided, increase the CABOMETYX dosage. Avoid St. John's wort.

USE IN SPECIFIC POPULATIONS

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

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

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; TKI=tyrosine kinase inhibitor.

*PFS was assessed by a retrospective blinded IRRC.[2]

References: 1. Data on file. Exelixis, Inc. IMS Health, October 2018. **2.** CABOMETYX® (cabozantinib) Prescribing Information. Exelixis, Inc, 2019. **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. 2018. 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.

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

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

Learn more at CABOMETYXhcp.com

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

1.1 Renal Cell Carcinoma

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

1.2 Hepatocellular Carcinoma

CABOMETYX is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hemorrhage

Severe and fatal hemorrhages occurred with CABOMETYX. The incidence of Grade 3 to 5 hemorrhagic events was 5% in CABOMETYX-treated patients.

Discontinue CABOMETYX for Grade 3 or 4 hemorrhage. Do not administer CABOMETYX to patients who have a recent history of hemorrhage, including hemoptysis, hematemesis, or melena.

5.2 Perforations and Fistulas

Fistulas, including fatal cases, occurred in 1% of CABOMETYX-treated patients. Gastrointestinal (GI) perforations, including fatal cases, occurred in 1% of CABOMETYX-treated patients.

Monitor patients for signs and 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 increased the risk of thrombotic events. Venous thromboembolism occurred in 7% (including 4% pulmonary embolism) and arterial thromboembolism occurred in 2% of CABOMETYX-treated patients. Fatal thrombotic events occurred in CABOMETYX-treated patients.

Discontinue CABOMETYX in patients who develop an acute myocardial infarction or serious arterial or venous thromboembolic events that require medical intervention.

5.4 Hypertension and Hypertensive Crisis

CABOMETYX can cause hypertension, including hypertensive crisis. Hypertension was reported in 36% (17% Grade 3 and <1% Grade 4) of CABOMETYX-treated patients.

Do not initiate CABOMETYX in patients with uncontrolled hypertension. Monitor blood pressure 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 or for hypertensive crisis.

5.5 Diarrhea

Diarrhea occurred in 63% of patients treated with CABOMETYX. Grade 3 diarrhea occurred in 11% of patients treated with CABOMETYX.

Withhold CABOMETYX until improvement to Grade 1 and resume CABOMETYX at a reduced dose for intolerable Grade 2 diarrhea, Grade 3 diarrhea that cannot be managed with standard antidiarrheal treatments, or Grade 4 diarrhea.

5.6 Palmar-Plantar Erythrodysesthesia

Palmar-plantar erythrodysesthesia (PPE) occurred in 44% of patients treated with CABOMETYX. Grade 3 PPE occurred in 13% of patients treated with CABOMETYX.

Withhold CABOMETYX until improvement to Grade 1 and resume CABOMETYX at a reduced dose for intolerable Grade 2 PPE or Grade 3 PPE.

5.7 Proteinuria

Proteinuria was observed in 7% of patients receiving CABOMETYX. Monitor urine protein regularly during CABOMETYX treatment. Discontinue CABOMETYX in patients who develop nephrotic syndrome.

5.8 Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) occurred in <1% of patients treated with CABOMETYX. ONJ can manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration or erosion, persistent jaw pain or slow healing of the mouth or jaw after dental surgery. Perform an oral examination prior to initiation of CABOMETYX and periodically during CABOMETYX. Advise patients regarding good oral hygiene practices. Withhold CABOMETYX for at least 28 days prior to scheduled dental surgery or invasive dental procedures, if possible. Withhold CABOMETYX for development of ONJ until complete resolution.

5.9 Wound Complications

Wound complications have been reported with CABOMETYX. Stop CABOMETYX at least 28 days prior to scheduled surgery. Resume CABOMETYX after surgery based on clinical judgment of adequate wound healing. Withhold CABOMETYX in patients with dehiscence or wound healing complications requiring medical intervention.

5.10 Reversible Posterior Leukoencephalopathy Syndrome

Reversible Posterior Leukoencephalopathy Syndrome (RPLS), a syndrome of subcortical vasogenic edema diagnosed by characteristic finding on MRI, can occur with CABOMETYX. 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.

5.11 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 clinically significant adverse reactions are discussed above and in the Warnings and Precautions section of the prescribing information: Hemorrhage, Perforations and Fistulas, Thrombotic Events, Hypertension and Hypertensive Crisis, Diarrhea, Palmar-plantar Erythrodysesthesia, Proteinuria, Osteonecrosis of the Jaw, Wound Complications, Reversible Posterior Leukoencephalopathy Syndrome

6.1 Clinical Trial Experience

The data described in the WARNINGS AND PRECAUTIONS section below reflect exposure to CABOMETYX as a single agent in 409 patients with RCC enrolled in randomized, active-controlled trials (CABOSUN, METEOR) and 467 patients with HCC enrolled in a randomized, placebo-controlled trial (CELESTIAL).

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.

Renal Cell Carcinoma

METEOR

The safety of CABOMETYX was evaluated in METEOR, a randomized, open-label trial in which 331 patients with advanced renal cell carcinoma received CABOMETYX 60 mg once daily and 322 patients received everolimus 10 mg once 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, in order of decreasing frequency, were: 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, lymphopenia, anemia, hypokalemia, and increased GGT.

The dose was reduced in 60% of patients receiving CABOMETYX and in 24% of patients receiving everolimus. Twenty percent (20%) of patients received CABOMETYX 20 mg once daily 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 leading to dose interruption occurred 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				
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				
Fatigue	56	9	47	7
Mucosal inflammation	19	<1	23	3
Asthenia	19	4	16	2
Metabolism and Nutrition				
Decreased appetite	46	3	34	<1
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysesthesia	42	8	6	<1
Rash [4]	23	<1	43	<1
Dry skin	11	0	10	0
Vascular				
Hypertension [5]	39	16	8	3
Investigations				
Weight decreased	31	2	12	0
Nervous System				
Dysgeusia	24	0	9	0
Headache	11	<1	12	<1
Dizziness	11	0	7	0
Endocrine				
Hypothyroidism	21	0	<1	<1
Respiratory, Thoracic, and Mediastinal				
Dysphonia	20	<1	4	0
Dyspnea	19	3	29	4
Cough	18	<1	33	<1
Blood and Lymphatic				
Anemia	17	5	38	16
Musculoskeletal and Connective Tissue				
Pain in extremity	14	1	8	<1
Muscle spasms	13	0	5	0
Arthralgia	11	<1	14	1
Renal and Urinary				
Proteinuria	12	2	9	<1

[1] One subject randomized to everolimus received cabozantinib.
[2] National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0
[3] Includes the following terms: abdominal pain, abdominal pain upper, and abdominal pain lower
[4] Includes the following 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 the following 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

Laboratory Abnormality	CABOMETYX (n=331)		Everolimus (n=322)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
	Percentage (%) of Patients			
Chemistry				
Increased AST	74	3	40	<1
Increased ALT	68	3	32	<1
Increased creatinine	58	<1	71	0
Increased triglycerides	53	4	73	13
Hypophosphatemia	48	8	36	5
Hyperglycemia	37	2	59	8
Hypoalbuminemia	36	2	28	<1
Increased ALP	35	2	29	1
Hypomagnesemia	31	7	4	<1
Hyponatremia	30	8	26	6
Increased GGT	27	5	43	9
Hematology				
Leukopenia	35	<1	31	<1
Neutropenia	31	2	17	<1
Anemia[1]	31	4	71	17
Lymphopenia	25	7	39	12
Thrombocytopenia	25	<1	27	<1

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase.
NCI CTCAE, Version 4.0
[1] Based on laboratory abnormalities

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 CABOMETYX 60 mg once daily and 72 patients received sunitinib 50 mg 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, 2 patients died due to gastrointestinal perforation, 1 patient had acute renal failure, and 1 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, increased ALT, 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

Adverse Reaction	CABOMETYX (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		
Diarrhea	10	11
Stomatitis	5	6
Nausea	3	4
Vomiting	1	3
Constipation	1	0
General		
Fatigue	6	17
Pain	5	0
Metabolism and Nutrition		
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 Tissue		
Palmar-plantar erythrodysesthesia	8	4
Skin ulcer	3	0
Vascular		
Hypertension[3]	28	21
Hypotension	5	1
Angiopathy	1	1
Investigations		
Increased ALT[2]	5	0
Weight decreased	4	0
Increased AST [2]	3	3
Increased blood creatinine [2]	3	3
Lymphopenia [2]	1	6
Thrombocytopenia [2]	1	11
Nervous System		
Syncope	5	0
Respiratory, Thoracic, and Mediastinal		
Dyspnea	1	6

Adverse Reaction	CABOMETYX (n = 78)	Sunitinib (n = 72)
	Grade 3-4[1]	Grade 3-4[1]
	Percentage (%) of Patients	
Dysphonia	1	0
Blood and Lymphatic		
Anemia	1	3
Psychiatric		
Depression	4	0
Confusional state	1	1
Infections		
Lung infection	4	0
Musculoskeletal and Connective Tissue		
Back pain	4	0
Bone pain	3	1
Pain in extremity	3	0
Arthralgia	1	0
Renal and Urinary		
Renal failure acute	4	1
Proteinuria	3	1

ALT, alanine aminotransferase; AST, aspartate aminotransferase

[1] NCI CTCAE Version 4.0

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

[3] Includes the following term: hypertension

Hepatocellular Carcinoma

The safety of CABOMETYX was evaluated in CELESTIAL, a randomized, double-blind, placebo-controlled trial in which 704 patients with advanced hepatocellular carcinoma were randomized to receive CABOMETYX 60 mg orally once daily (n=467) or placebo (n=237) until disease progression or unacceptable toxicity. The median duration of treatment was 3.8 months (range 0.1 – 37.3) for patients receiving CABOMETYX and 2.0 months (range 0.0 – 27.2) for patients receiving placebo. The population exposed to CABOMETYX was 81% male, 56% White, and had a median age of 64 years.

Adverse reactions occurring in ≥ 25% of CABOMETYX-treated patients, in order of decreasing frequency were: diarrhea, decreased appetite, PPE, fatigue, nausea, hypertension, and vomiting. Grade 3-4 adverse reactions which occurred in ≥ 5% of patients were PPE, hypertension, fatigue, diarrhea, asthenia, and decreased appetite. There were 6 adverse reactions leading to death in patients receiving CABOMETYX (hepatic failure, hepatorenal syndrome, esophagobronchial fistula, portal vein thrombosis, pulmonary embolism, upper gastrointestinal hemorrhage).

The median average daily dose was 35.8 mg for CABOMETYX. The dose was reduced in 62% of patients receiving CABOMETYX; 33% of patients required a reduction to 20 mg daily. The most frequent adverse reactions or laboratory abnormalities leading to dose reduction of CABOMETYX were: PPE, diarrhea, fatigue, hypertension, and increased AST. Adverse reactions leading to dose interruption occurred in 84% patients receiving CABOMETYX. Adverse reactions leading to permanent discontinuation of CABOMETYX occurred in 16% of patients. The most frequent adverse reactions leading to permanent discontinuation of CABOMETYX were PPE (2%), fatigue (2%), decreased appetite (1%), diarrhea (1%), and nausea (1%).

Table 4. Adverse Reactions Occurring in ≥ 5% of CABOMETYX-Treated Patients in CELESTIAL[1]

Adverse Reaction	CABOMETYX (n = 467)		Placebo (n = 237)	
	All Grades[2]	Grade 3-4	All Grades[2]	Grade 3-4
	Percentage (%) of Patients			
Gastrointestinal				
Diarrhea	54	10	19	2
Nausea	31	2	18	2
Vomiting	26	<1	12	3
Stomatitis	13	2	2	0
Dyspepsia	10	0	3	0
General				
Fatigue	45	10	30	4
Asthenia	22	7	8	2
Mucosal inflammation	14	2	2	<1
Metabolism and Nutrition				
Decreased appetite	48	6	18	<1
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysesthesia	46	17	5	0
Rash[3]	21	2	9	<1
Vascular				
Hypertension[4]	30	16	6	2
Investigations				
Weight decreased	17	1	6	0
Nervous System				
Dysgeusia	12	0	2	0
Endocrine				
Hypothyroidism	8	<1	<1	0
Respiratory, Thoracic, and Mediastinal				
Dysphonia	19	1	2	0
Dyspnea	12	3	10	<1
Musculoskeletal and Connective Tissue				
Pain in extremity	9	<1	4	1
Muscle spasms	8	<1	2	0

[1] Includes terms with a between-arm difference of ≥ 5% (all grades) or ≥ 2% (Grade 3-4)

[2] NCI CTCAE Version 4.0

[3] Includes the following terms: rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, dermatitis, dermatitis acneiform, dermatitis contact, dermatitis diaper, dermatitis exfoliative, dermatitis infected

[4] Includes the following terms: hypertension, blood pressure diastolic increased, blood pressure increased

Table 5. Laboratory Abnormalities Occurring in ≥ 5% of CABOMETYX-Treated Patients in CELESTIAL[1]

Laboratory Abnormality	CABOMETYX N=467		Placebo N=237	
	All Grades	Grade 3-4	All Grades	Grade 3-4
	Percentage of Patients			
Chemistry				
Increased LDH	84	9	29	2
Increased ALT	73	12	37	6
Increased AST	73	24	46	19
Hypoalbuminemia	51	1	32	1
Increased ALP	43	8	38	6
Hypophosphatemia	25	9	8	4
Hypokalemia	23	6	6	1
Hypomagnesemia	22	3	3	0
Increased amylase	16	2	9	2
Hypocalcemia	8	2	0	0
Hematology				
Decreased platelets	54	10	16	1
Neutropenia	43	7	8	1
Increased hemoglobin	8	0	1	0

[1] Includes laboratory abnormalities with a between-arm difference of ≥ 5% (all grades) or ≥ 2% (Grade 3 4)

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, blood lactate dehydrogenase

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on CABOMETYX

Strong CYP3A4 Inhibitors

Coadministration of a cabozantinib capsule formulation with a strong CYP3A4 inhibitor increased the exposure of cabozantinib, which may increase the risk of exposure-related adverse reactions. Avoid coadministration of CABOMETYX with strong CYP3A4 inhibitors. Reduce the dosage of CABOMETYX if coadministration with strong CYP3A4 inhibitors cannot be avoided. Avoid grapefruit or grapefruit juice which may also increase exposure of cabozantinib.

Strong CYP3A Inducers

Coadministration of a cabozantinib capsule formulation with a strong CYP3A4 inducer decreased the exposure of cabozantinib, which may reduce efficacy. Avoid coadministration of CABOMETYX with strong CYP3A4 inducers. Increase the dosage of CABOMETYX if coadministration with strong CYP3A4 inducers cannot be avoided. Avoid St. John's wort which may also decrease exposure of cabozantinib.

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 *(see Data)*. Advise pregnant women of the potential risk to a fetus.

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 area under the curve [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 child or milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with CABOMETYX and for 4 months after the final dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating CABOMETYX.

Contraception

CABOMETYX can cause fetal harm when administered to a pregnant woman.

Females

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 Toxicity Data

Juvenile rats were administered cabozantinib 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 ≥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 a dose of 2 mg/kg (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 CABOSUN and METEOR, 41% of 409 patients treated with CABOMETYX were age 65 years and older, and 8% were 75 years and older. In CELESTIAL, 49% of 467 patients treated with CABOMETYX were age 65 years and older, and 15% were 75 years and older.

No overall differences in safety or effectiveness were observed between these patients and younger patients.

8.6 Hepatic Impairment

Increased exposure to cabozantinib has been observed in patients with moderate (Child-Pugh B) hepatic impairment. Reduce the CABOMETYX dose in patients with moderate hepatic impairment. Avoid CABOMETYX in patients with severe hepatic impairment (Child-Pugh C), since it has not been studied in this population.

8.7 Renal Impairment

No dosage adjustment is recommended 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 following administration of another formulation of cabozantinib; a patient inadvertently took twice the intended dose for 9 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).

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

Perforations and fistulas: 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: Advise patients to contact their healthcare provider before any planned surgeries, including dental surgery.

Reversible posterior leukoencephalopathy syndrome: Advise patients to immediately contact their health care provider for new onset or worsening neurological function.

Drug interactions: Advise patients to inform their healthcare provider of all prescription or nonprescription medications, vitamins or herbal products. Inform patients to avoid grapefruit, grapefruit juice, and St. John's wort.

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 females of reproductive potential to use effective contraception during treatment with CABOMETYX and for 4 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 take CABOMETYX at least 1 hour before or at least 2 hours after eating.

This brief summary is based on the CABOMETYX Prescribing Information
Revision 01/2019
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About the Cover
This image illustrates an example of multi-modal collection for a radical nephrectomy specimen and how it could be integrated into a biospecimen banking system. The points suggest how a surgical sample could be processed for inclusion in multiple studies such as a RCC tissue microarray, multi-region proteomic sampling, larger core biopsies for patient-derived xeno-grafts, or for bulk tissue acquisition for organoids and other larger-scale models and analyses. (Courtesy of John Leppert, MD)

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KCJ EDITOR'S MEMO

Remembering Professor Martin Gore, 1951–2019

Tributes pour in, honoring him as 'force of nature,' brilliant clinician


Robert A. Figlin, MD

Although most of the 4500 or so attendees at this year's GU ASCO meeting may not have been aware, the death of Professor Martin Gore cast a long shadow over the proceedings for those of us who knew this brilliant clinician and outstanding human being. Dr Gore, 67, one of the UK's leading oncologists, died in January after experiencing total organ failure following a yellow fever vaccination, an extremely rare complication.

A report in the *Journal of Travel Medicine* found that between 2007 and 2013, there were just under four cases of serious adverse effects from the vaccine per 100,000 doses. This increased to 6.5 per 100,000 for those aged between 60 and 69, and 10.3 per 100,000 for those aged 70 and above. The vaccination is recommended for anyone visiting Sub-Saharan Africa, South and Central America, and the Caribbean.


Professor Martin Gore

Dr Gore, who inspired generations of physicians, was a professor at the Institute of Cancer Research and former Medical Director of the Royal Marsden Hospital, London. Prof Mel Greaves, from The Institute of Cancer Research, said: "Martin was something of a force of nature, very energetic, clear thinking and compassionate." In the following recollection, Professor Tim Eisen highlights his memories of Dr Gore.

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Robert A. Figlin, MD
Editor-in-Chief

EDITOR'S MEMO

(continued from page 6)

A Tribute From Prof Tim Eisen: Remembering His 'Extraordinary Array of Talents'


Professor Tim Eisen

I first met Martin when I was being interviewed for a junior doctor's job at the Royal Marsden Hospital in London. Martin's sense of humor and infectious enthusiasm were immediately obvious. It took me a little longer to recognize his extraordinary array of talents: Martin combined great self-confidence with a real sensitivity for how others felt, clear and decisive thinking and a penetrating intelligence.

One of Martin's most endearing traits was his ability to laugh at himself. After any ludicrous or embarrassing event, there would always be a theatrical and exaggerated rendition which entertained and instructed. Nobody should have been fooled by the stream of wit and humor. Martin could be as direct and firm as the situation demanded. Martin made an international impact in ovarian cancer, melanoma and renal cancer. He was a long-serving and extremely successful Medical Director of the Royal Marsden Hospital and in recent years, he took leading roles advising the UK government on tricky subjects such as gene therapy, biological security and enquiries into healthcare failings in the NHS.

Martin was fabulously loyal to the Marsden. Two things rang particularly true about the press coverage of Martin's death; the first was a description of him as the beating heart of the Marsden and the second was that, when the terrible news spread, many of the cleaning staff were in tears. Martin appreciated everybody who was part of the Marsden; his authenticity as a leader was palpable and people loved him for it.

What do I miss most about Martin? I miss the friendship of this funny, brilliant, kind and unforgettable man.

Tim Eisen
Professor of Medical Oncology
University of Cambridge and Vice President
Oncology Early Clinical Projects
AstraZeneca

Essential Peer-Reviewed Reading in Kidney Cancer

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

Metastatic clear-cell renal cell carcinoma with a long-term response to sunitinib: a distinct phenotype independently associated with low PD-L1 expression. Kammerer-Jacquet SF, Brunot A, Lefort M, at al. *Clin Genitorurin Cancer*. 2019 Feb 4; pii: S1558-7673(18)30716-X. doi: 10.1016/j.clgc.2019.01.014.
Summary: Long-term responders (LTRs) are defined by at least 18 months of response to sunitinib in metastatic clear-cell renal cell carcinoma (ccRCC). The phenotype of these tumors has never been explored. In a retrospective and multicenter study, 90 ccRCCs of patients with metastatic disease were analyzed. Immunohistochemistry (carbonic anhydrase IX, vascular endothelial growth factor, c-MET, programmed death-ligand 1 [PD-L1], and PD-1) and VHL status were performed. Progression-free survival and overall survival were calculated from sunitinib introduction and from progression. LTRs and their corresponding tumors were compared with others using univariate and multivariate analysis.

Twenty-eight patients were LTRs. They had a median progression-free survival of 28 months vs 4 months for other patients. Similarly, LTRs had a median overall survival of 49 months vs 14 months, even from progression (median, 21 vs. 7 months). They were associated with a favorable or intermediate risk (International Metastatic Renal Cell Carcinoma Database Consortium model) and less liver metastasis. They experienced more frequent complete or partial responses at the first radiologic evaluation. The corresponding ccRCCs were associated with less nucleolar International Society for Urological Pathology grade 4 and hilar fat infiltration. They were also associated with low PD-L1 expression.
Conclusion: Primary tumor characteristics of LTRs were studied for the first time and demonstrated a different phenotype. Interestingly, they were characterized by low expression of PD-L1, suggesting a potentially lower impact of targeted immunotherapy in these patients.

Cabozantinib in advanced non-clear-cell renal cell carcinoma: a multicentre, retrospective, cohort study. Martinez Chanzá N, Xie W, Asim Bilen M, et al. *Lancet Oncol*. 2019 Feb 28. pii: S1470-2045(18)30907-0. doi: 10.1016/S1470-2045(18)30907-0.
Summary: This study analyzed the antitumor activity and toxicity of cabozantinib in advanced non-clear-cell renal cell carcinoma. This was a multicenter, international, retrospective cohort study of patients with metastatic nccRCC treated with oral cabozantinib during any treatment line at 22 centers: 21 in the US and one in Belgium. The main objectives were to estimate the proportion of patients who achieved an objective response, time to treatment failure, and overall survival after treatment. Of 112 identified patients with nccRCC, 66 (59%) had papillary histology, 17 (15%) had Xp11.2 translocation histology, 15 (13%) had unclassified histology, ten (9%) had chromophobe histology, and four (4%) had collecting duct histology. The proportion of patients who achieved an objective response across all histologies was 30 of 112 patients. At a median follow-up of 11 months (IQR 6-18), median time to treatment failure was 6·7 months, median progression-free survival was 7·0 months (5·7-9·0), and median overall survival was 12·0 months (9·2-17·0). The most common adverse events of any grade were fatigue (58 [52%]), and diarrhea (38 [34%]). The most common grade 3 events were skin toxicity (rash and palmar-plantar erythrodysesthesia; five [4%]) and hypertension (four [4%]). No treatment-related deaths were observed. Across 54 patients with available next-generation sequencing data, the most frequently altered somatic genes were CDKN2A (12 [22%]) and MET (11 [20%]) with responses seen irrespective of mutational status.
Conclusion: This real-world study provides evidence supporting the antitumor activity and safety of cabozantinib across non-clear-cell renal cell carcinomas. Continued support of international collaborations and prospective ongoing studies targeting nccRCC carcinoma subtypes and specific molecular alterations are warranted to improve outcomes across these rare diseases with few evidence-based treatment options.

Sarcomatoid renal cell carcinoma: population-based study of 879 patients. Alevizakos M, Gaitanidis A, Nasioudis D, et al. *Clin Genitourin Cancer*. 2019 Jan 17. pii: S1558-7673(19)30014-X. doi:10.1016/j.clgc.2019.01.005.
Summary: This study accessed the National Cancer Institute's Surveillance, Epidemiology, and End Results database (2010-2015) and extracted data on patients with sRCC. Median, 1-, 3-, and 5-year disease-specific survival (DSS) probabilities were estimated to evaluate variables associated with nephrectomy and DSS. A total of 879 patients with sRCC were identified; 60.9% patients had stage IV disease at diagnosis, and the median tumor size was 8.3 cm (interquartile range, 5.5-12 cm). The 5-year DSS were 77.7%, 67.8%, 35.4%, and 3.5% for patients with stage I, II, III, and IV disease at diagnosis, respectively; median DSS was 9 months (interquartile range, 4-42 months) for the entire cohort. Older age higher tumor stage and performance of nephrectomy were found to independently affect DSS.
Conclusion: In the largest sRCC cohort to date, the re-

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

New KCJ Website Will Offer Exciting Resource With Impact, Analyses to Unpack Emerging Data

NEW YORK—Where do you go for reliable, insightful, and late-breaking news online? Beginning April 15, the *Kidney Cancer Journal* will unveil dramatic changes to its website, providing readers with a new dimension of content all obtainable digitally. From a regularly updated newsfeed to analyses following articles in the journal, readers will have a dynamic source of information that digs behind the headlines to unpack the most impactful information, bringing you results with translational importance. For 17 years the journal has established a reputation as the most comprehensive source on renal cell carcinoma trends. By enhancing the website, the journal will keep you up to date on late-breaking news while analyzing its significance.

A Demographic Snapshot: Who Attends GU ASCO Meeting?

SAN FRANCISCO—The American Society of Clinical Oncology (ASCO) offers a quick summary on who attends its GU meeting. The demographics for 2019 are expected to be similar to last year's results when 4500 attended the meeting. Here is the breakout of who attends:

- Professionals—4150
- Exhibitors—284
- Spouse, Guest, Media—66
- Domestic Attendees—50%
- International Attendees—50%

TOP 5 COUNTRIES

- United States—2057
- France—210
- Canada—204
- United Kingdom—161
- Germany—153
- 65 Other Countries—1365

FDA Gives Priority Status to Avelumab-Axitinib Combination

SILVER SPRING, MD—The FDA has accepted for priority review a supplemental Biologics License Application for Merck's Bavencio (avelumab) in combination with Inlyta (axitinib) for patients with advanced renal cell carcinoma (RCC). The submission is based on data from the pivotal Phase III JAVELIN Renal 101 trial, in which 30 clinical programs and more than 9,000 patients evaluated across more than 15 different tumor types.In addition to RCC, these tumor types include breast, gastric/gastro-esophageal junction, and head and neck cancers, Merkel cell carcinoma, non-small cell lung cancer, and urothelial carcinoma. Clear cell carcinoma, accounts for approximately 70% of all RCC cases, with an estimated 73,820 new cases of kidney cancer expected to be diagnosed in the US in 2019.

Tivozanib, Still Seeking FDA Approval, Scores Favorable Results in Phase 3

Tivozanib, a tyrosine kinase inhibitor with a troubled history at the FDA despite its approval in Europe, is making progress in a Phase 3 trial that may yet set the stage for the drug to become a part of treatment selection in the US.

Patients with refractory metastatic renal cell carcinoma (mRCC) have better outcomes when treated with tivozanib compared with sorafenib, according to study findings presented at the 2019 Genitourinary Cancers Symposium. In the TIVO-3 phase 3 trial (ClinicalTrials.gov Identifier: NCT02627963), which compared the drugs in patients with mRCC who had received 2 or 3 prior systematic therapies that failed, median progression-free survival (PFS) was 5.6 months (95% CI, 7.3-5.3) among patients who received tivozanib compared with 3.9 months (95% CI, 5.6-3.7) for patients treated with sorafenib, lead investigator Brian I. Rini, MD, of the Cleveland Clinic Taussig Cancer Institute, reported. Tivozanib treatment was associated with a significant 27% decreased risk of disease progression (hazard ratio 0.73; P =.02) compared with sorafenib therapy. In addition, the PFS rate at 2 years was higher in the tivozanib compared with the sorafenib arm (18% vs 5%). Furthermore, tivozanib-treated patients had a higher objective response rate compared with sorafenib recipients (18% vs 8%).

Grade 3 treatment-related adverse events occurred in 44% of patients in the tivozanib group and 55% of the sorafenib arm. In addition, a smaller proportion of patients in tivozanib group required a dose reduction compared with the sorafenib group (24% vs 38%) or interruption of treatment (48% vs 63%) due to an adverse event. Tivozanib-treated patients also were less likely to discontinue treatment (21% vs 29%).

Tivozanib has been included as a first-line treatment recommendation for advanced RCC in new European Society of Medical Oncology (ESMO) clinical practice guidelines for RCC, published last month. Tivozanib is recommended as a first-line treatment option for people with advanced clear cell RCC of good (favorable) risk or intermediate risk.

After the CARMENA Trial: Do Patients Still Want a Nephrectomy? The Answer Is Yes

Conducted over eight years, enrolling 450 patients at multiple centers in Europe, the CARMENA (Cancer du Rein Metastatique Nephrectomie et Antiangiongeniques) trial demonstrated that systemic therapy using sunitinib alone is not worse than cytoreductive nephrectomy (CN) plus sunitinib in metastatic RCC in an intention to treat analysis (hazard ratio HR): 0.89, 95% confidence interval (CI), 0.71-1.10) But what do patients think? Are their concerns in line with the physicians who manage their disease?

The Kidney Cancer Research Alliance (KCCure) conducted a survey among kidney cancer patients. The short

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Supporting Kidney Cancer Research: Lessons Learned Establishing The Stanford Kidney Cancer Biospecimen Repository

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Abstract

Advancing our understanding of kidney cancer relies on the acquisition of biological specimens from patients with the disease. The increasing complexity of cancer biology studies necessitates a "team science" approach, leveraging input from a multidisciplinary team and often requiring multiple methods for acquiring and preparing biospecimens. Researchers face many challenges when developing infrastructure to obtain high-quality specimens, including limited access to specimens due to regulatory requirements and institutional barriers, and a lack of familiarity with clinical care environments. Clinicians also face challenges when working to collect samples outside of an individual practice, including access to multiple locations and other sub-specialty care services. The collecting of high-quality biospecimens itself is challenging, as it is important to consider patient characteristics, pre-analytic variables, collection protocols, specimen handling, and data management. The purpose of this paper is to detail our experience addressing these challenges while developing the infrastructure for a kidney cancer biospecimen repository. We believe that sharing solutions to these challenges at a single institution may assist others developing similar programs, and will aid in fostering future efforts for collaborative group banking efforts with specimen and data harmonization.

Key words: Renal cell carcinoma, biospecimen, repository, biopsy, biology, collection, specimen handling, research protocol, tissue banking, Clinical Research Coordinator.

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Acknowledgements: This manuscript is dedicated to the memory of Larry Lulofs, and to the hundreds of patients with renal cell carcinoma who have selflessly donated their tissues to support our research efforts in hopes of improving treatments for future patients.

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Introduction

Renal cell carcinoma (RCC, kidney cancer) poses a daunting research and clinical challenge. RCC is not a single disease, but represents a group of cancers with distinct biology that happen to arise from the kidney. Moreover, each variant of RCC can manifest across a broad spectrum of risk – from slow-growing indolent lesions, to rapidly growing cancers with high metastatic potential. The study of RCC specimens has played an integral part in advancing our understanding of the biology of RCC, and has led to the global improvement in our ability to care for patients. Despite these advancements, significant opportunities remain for basic and translational research utilizing human RCC biospecimens.[1] The Urology Care Foundation National Urology Research Agenda highlights the urgency of establishing "biospecimen repositories of well documented disease and normal tissue" in the National Urology Research Agenda.[3] The importance of high-quality biospecimens is well established within the cancer and RCC research communities.[4,5] The practice of biospecimen collection must continue to evolve to meet the needs of RCC researchers.[2] To continue to improve biospecimen repositories, best practices have been proposed to ensure the collection of samples that support reproducible high-quality research.[6,7]

The Stanford Kidney Cancer Research Program is an interdisciplinary group of physicians and basic scientists who are dedicated to pioneering research studies to increase knowledge of the biology of, and improve treatments for, RCC. In order to support this growing research enterprise, we have collaborated to build the infrastruc-

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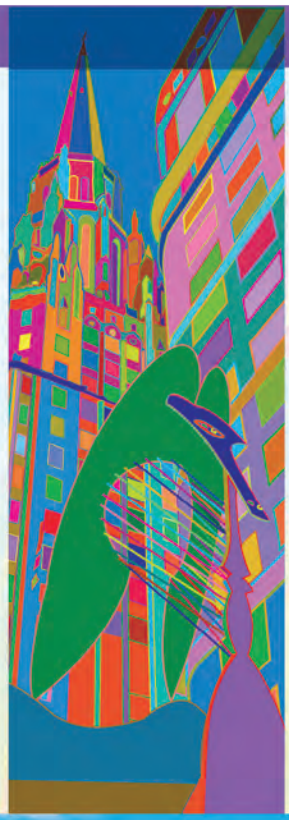

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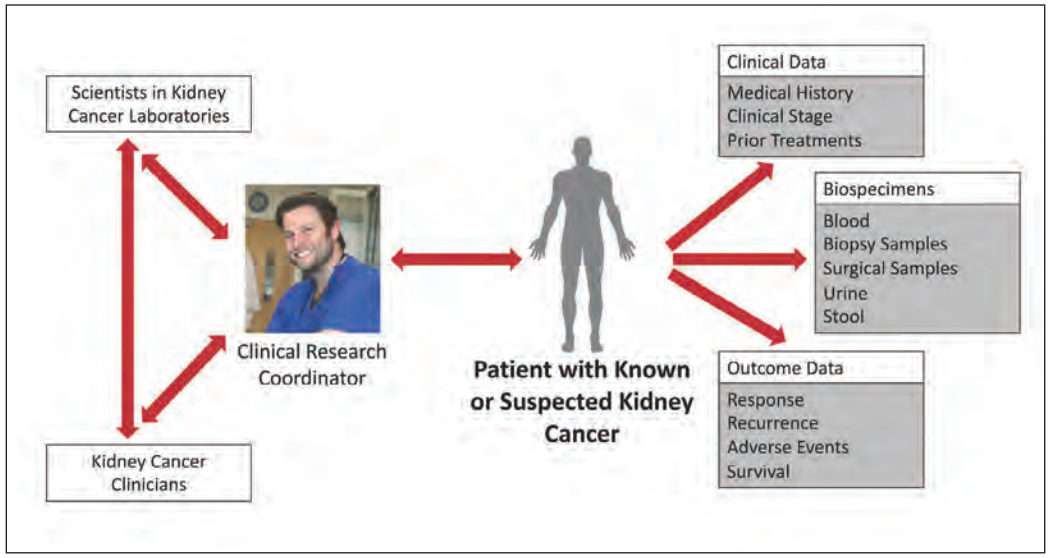

Figure 1. Schematic of the organization of the Stanford prospectively collected biospecimen repository.

ture necessary to collect a wide range of RCC biospecimens. Like many other institutions, we have addressed administrative and regulatory issues in building this program, and when coordinating these efforts with existing programs.

In this publication, we aim to share our experience within Stanford University and the VA Palo Alto Health Care System. Our intent is to generate discussion to broadly support RCC biospecimen collection and research, and to foster efforts for specimen and data harmonization across collaborative groups focusing on advancing our understanding of RCC.

Personnel

A research enterprise devoted to the acquisition of biological specimens from patients with RCC requires key personnel to be both useful and efficient. At Stanford, the personnel who are crucial to our biospecimen banking efforts are the Principal Investigators, Clinical Research Coordinators, basic scientists, and other clinicians treating patients with RCC. (**Figure 1**)

Principal Investigator

We have adopted several approaches to acquiring and organizing human-subjects research protocols for kidney cancer biospecimen collection that are approved by the Stanford Institutional Review Board (IRB). While many institutions (including our own) maintain cancer tissue banks, or umbrella protocols to collect tissue across many disease states, we have worked to develop specific RCC biospecimen collection protocols led by Principal Investigators (PIs) who are clinicians that specialize in the management and care of patients with RCC. As a clinician, the PI will have a good working understanding of the clinical environment, and the complexities of conducting research in that environment, while remaining an advocate for each patient. Furthermore, clinically informed PIs will recognize opportunities for the research team to acquire biological specimens needed to answer timely clinical questions. With this knowledge and experience, a clinician-PI is also best suited to guide and train Clinical Research Coordinators to assist in the clinical sample and data collection effort.

This approach has resulted in a research protocol with a Urologist (JTL) as PI that focuses on obtaining biospecimens from patients at the time of clinical procedures, such as tissue from nephrectomies, metastasectomies, and image-guided biopsies, as well as blood and urine samples from patients with localized disease. Similarly, a research protocol is also in place with a medical oncologist (ACF) as PI, which focuses on serial blood and urine sampling, and collecting tumor biopsies from patients receiving systemic therapies to treat advanced disease. Finally, there remain broad protocols designed to enroll all patients receiving care through the Urology department, as well as a general tissue-banking protocol that is managed by the Stanford Cancer Institute. While these latter services follow a "banking model" and are designed to bank biospecimens from all patients, we have taken a more targeted approach, prospectively collecting tissues for specific research questions and also serving as a repository for future analyses.[8] We have streamlined our RCC protocols to ensure that patients avoid consent fatigue, and that relevant biospecimens can be collected (even as patients transition from localized to advanced disease) without requiring enrollment on additional protocols. Further, we have intended for the RCC-specific and institutional generalized tissue banking protocols to operate symbiotically, maximizing biospecimen banking in the support of RCC research.

Clinical Research Coordinator

We have designed a unique hybrid Clinical Research Coordinator (CRC) position that combines capacities typical of a research coordinator with those of a research assistant. We attribute much of our success in obtaining specimens to this hybrid CRC position, which empowers the CRC to participate in every aspect of the tissue collection process. The CRC is responsible for tasks commonly assigned to CRC's at other institutions, including writing protocols that allow for biospecimen acquisition, maintaining regulatory approvals, and managing study data. The CRC also obtains informed consent from participants in clinical environments, such as the outpatient clinic, inpatient wards, and pre-operative holding area. What we believe is unique at our institution, however,

is that the CRC is positioned in the operating room during interventional procedures that allow for tissue harvest (nephrectomies, metastasectomies, image-guided biopsies, and ablations). For many researchers and research coordinators, clinical environments such as the operating room are daunting. This perceived, and sometimes real, barrier between the research environment and clinical care settings can impede specimen collection efforts. By being present in the operating room and interventional radiology suite, the CRC is able to communicate with the clinical staff to answer questions regarding specimen acquisition, record critical pre-analytic variables, and coordinate with research teams waiting to receive the specimens. If needed for a particular assay, our CRC's are also able to process specimens utilizing skills acquired from past laboratory bench-based research experience. This allows for highly specialized collection protocols that extend our capacity beyond traditional tissue banks.

Due to this unique hybrid position, we believe the CRC must be an individual who is capable of bridging the gap between the research laboratories using the tissue specimens and the clinical environments from which the specimens are acquired. Most importantly, the CRC must be skilled in communicating with patients with cancer and their families, so they do not incur additional stress during their treatments. The CRC also must build collegial relationships with both medical and research staff, and maintain familiarity and competence in clinical environments like the operating room and gross pathology work room.

In order for a CRC to be effective in this role, he or she must be given the tools to operate with a high degree of independence. Such tools include access to the clinical environments where patients can be consented and tissues can be obtained (clinics, operating rooms, pathology gross rooms, interventional radiology suites, and hospital wards), and access to resources to identify potential cases, look up surgery times and patient visits, acquire clinical data on research patients, and perform proper research documentation. We have had CRCs shadow PIs in the operating room during training, and work with the PI in the pathology gross room to acquire tissue specimens until the CRC becomes comfortable performing these duties independently. Similarly, the CRCs have shadowed PIs in the urologic and medical oncology clinics, learning about the patient experience as well as relevant kidney cancer biology and treatment courses. The Stanford Cancer Clinical Trials Office (CCTO) has provided training for the regulatory affairs aspect of the CRC's duties. The training in regulatory affairs and conduct of research that a CCTO can provide is invaluable in ensuring that a biospecimen harvesting research protocol is legally and ethically compliant.

Research Scientists

The basic scientists and laboratories involved in the Stanford Kidney Cancer Research Program are the end users of the tissue specimens acquired, and are actively involved in this prospective collection model. Research laboratories interested in studying RCC approach either the PI or CRC with clinically relevant hypotheses, and propose the biospecimens that would be required to test them. In doing so, the research scientists provide crucial information regarding acquisition, processing, and storage conditions required to maintain the fidelity of the specimens and eliminate variability in the research assays for which they will be used. In this way, basic scientists at our institution play an integral role (along with the CRC) in designing tissue acquisition protocols. We have had success designating a single member of the research team to act as a point of contact for the CRC. We also encourage discussion of protocols and strategies in our bi-weekly Stanford Kidney Cancer Research Program conference. This allows for the pertinent information regarding the specimen needs of the laboratory to be communicated, and allows the CRC to help identify upcoming cases or clinical encounters to quickly satisfy the group's tissue needs with specimens acquired under the optimal conditions. We have found that this level of communication allows the CRCs to provide specialized collection services not available through our institutional programs (e.g. collection of fresh tissue using core or fine-needle aspirate biopsies, multi-region tissue sampling, or collections in specific medium required for experiments). Moreover, this level of access to specimens has assisted with recruiting cancer biology laboratories to study RCC, as they often face challenges in acquiring biospecimens when studying other cancer types.

Clinicians

Treating patients with RCC requires a team that includes surgeons, oncologists, interventional radiologists, radiologists, and pathologists. Our research team involves all interested clinicians from these disciplines to maximize the acquisition of specimens, and increase the likelihood of acquisition of rare specimens. To do this, we have included multiple urologists and medical oncologists as study co-investigators on specimen acquisition protocols. Our protocol also includes pathologists as co-investigators to assist with the acquisition of tissue specimens from the gross room and re-review of histology when necessary. We encourage clinicians to also attend the aforementioned bi-weekly meetings to discuss research in progress. This has fostered trust among clinicians such that they feel comfortable in approaching their patients for enrollment to the studies, and are willing to participate in biospecimen collection even if it requires additional time and effort.

Designing Multi-Modal Biospecimen Collection Research Protocols

We have worked with the IRB to create protocols that allow collection of multiple specimen types (e.g. tissue, blood, and urine) at serial timepoints throughout the patient's clinical course. In order to obtain permission to

collect different types of biospecimens in a single protocol, we have designed a "check box system". With this system, a patient can opt in or out of providing certain biospecimens by initialing next to each procedure outlined in the consent. This gives patients the flexibility to participate in ways that they are most comfortable. For example, a patient may consent to donating tissue harvested after a surgery is complete, but not consent to blood collection at the time of surgery. We have found that the check box system in our consent reduces patients' anxiety associated with participating in the research study, and has increased our accrual.

Our comprehensive approach to collecting specimens has also provided the opportunity for some less common tissue collection strategies not available through generalized banking programs like the Stanford Tissue Bank. For example, a radical nephrectomy specimen could provide multi-region sampling as well as an 8mm core biopsy for preparation of xenograft models. Similarly, our prospective approach facilitates blood collections during routine clinical draws as well as research-only collections.

Practical Aspects of Specimen Acquisition

Though aspects of a biospecimen acquisition protocol will vary by institution and by research question, it is universally necessary for the specimens acquired to be collected in a way that minimizes artifact and preserves their biology to the highest degree possible, and that all aspects of collection are documented. An additional benefit of positioning a dedicated CRC where the specimen is collected is that it affords the research team the ability to record and systematically test critical pre-analytic variables that may influence the fidelity of the specimen. These include patient-level factors (e.g. specific comorbidities, prior RCC treatments), as well as pre-analytic variables specific to the procedure and tissue of interest (e.g. warm ischemia time, blood loss or hypotension during the procedure, the stabilization media used, transport and storage temperature, processing time).[5] To accomplish this, the CRC carries a tissue harvesting kit to every case. The kit contains the required specimen preparation tools, but also specialized methods for documenting collection efforts, such as marking pins to denote the region where tissue is harvested from during multi-region sampling, as well as a camera to capture relevant images of the tissue harvest that can be utilized later to identify areas of gross necrosis, fibrotic tissue, and variant histology. **Figure 2** illustrates some aspects of biospecimen collection, and how a surgical sample could be processed for inclusion in multiple studies such as a RCC tissue microarray,[9,10] multi-region proteomic sampling,[11] larger core biopsies for patient-derived xenografts,[12-17] or for bulk tissue acquisition for organoids and other larger-scale models and analyses.[18] Utilizing this approach, we have acquired specimens from 360 resected RCC tumors, with multi-region sampling in 312 cases. We also collect paired normal tissue in all cases when possible.

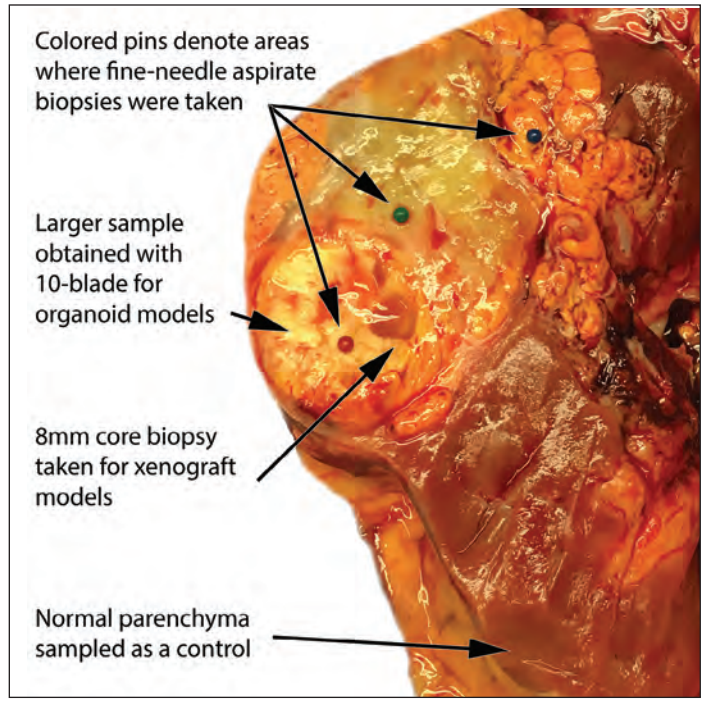

Figure 2. An example of multi-modal collection for a radical nephrectomy specimen.

Similarly, we prefer the CRC to also be present in the endoscopy and radiology suites throughout procedures involving image-guided biopsies. By being present in this way, the CRC can ensure that the specimen is properly labelled if taken from multiple locations, acquired and stored in the proper medium, and that aspects of the acquisition are documented (e.g. core vs. fine needle aspiration).[19] The actual presence of the CRC during the biopsy also assures that any questions that arise regarding the research specimens can be immediately addressed, increasing the rate of successfully acquired research biopsies. To date, we have acquired tissue specimens using CT, ultrasound, or endoscopic guidance from 26 participants.

Because clinical and research blood draws can occur in multiple laboratories and even multiple campuses, it is not possible for the CRC to be present for each blood collection in the same fashion. To ensure that research collections occur regardless of the location, the CRC coordinates and facilitates the placement of research blood draw orders in the patient's electronic medical record. A research blood draw kit is assembled with blood collection tubes specific to the needs of each assay. With the orders is a set of instructions provided to the phlebotomist or nurse drawing the blood, which details the conditions under which the blood should be stored, and instructs the person drawing the blood to record the draw time and page the CRC as soon as the blood is drawn so time-sensitive samples can be processed quickly. With this coordinated effort, blood can be collected and distributed to multiple laboratories investigating different aspects of RCC. Examples of specialized studies using blood collections include the isolation of

Figure 3. Example screenshot from our REDCap database. A) Research data is organized into instruments that include enrollment/regulatory data, clinical data, and specimen data. B) Customizable reports allow for specific data to be queried, shared, or exported for analysis. C) Pre-analytical variables for specimen collection can be included for each specimen. D) Media storage allows for attached photographs of specimens, or clinical image files to be attached for each specimen. E) The description of the photo can be included to note specimen characteristics.

circulating tumor cells, plasma banking and cryopreservation of PBMCs, and the development of novel blood-based diagnostic assays. Our protocols also allow for blood to be collected at serial time points, with specimens being collected at the time of routine clinical lab testing, drawn from intravenous ports or lines at the time of treatment or surgery, and dedicated research-only blood sampling that is independent of a routine lab draw. Together, these efforts have resulted in a repository of 1084 total blood samples collected from 344 participants (312 patients with RCC; 32 non-cancer controls), with 227 patients contributing serial samples throughout the course of their treatment.

Data Management

Equally as important as strong personnel and well-written protocols is a means by which to organize the tremendous amount of data collected. At Stanford, we utilize three databases in our research effort: a patient enrollment database, an institutional RCC clinical database, and a specimen database. Each resource has a specific purpose to meet the needs of the Kidney Cancer Research Program. Most importantly, all are encrypted and secured, allowing for the storage of Protected Health Information crucial to the clinical and translational aspects of the research effort.

Enrollment Database

The enrollment database tracks the screening, consent, enrollment, and withdrawal of patients from research protocols. The Stanford Cancer Institute utilizes OnCore v14.2 (Forte Research Systems, Madison, WI) as the enrollment database. This resource assigns each participant a study ID for specimen tracking and blinding, integrates with the electronic health record to pull participant demographic information, records when patients were consented and with what version of the protocol, and can track survival outcomes. It also allows for researchers to record if patients withdraw from the study and for what reason, along with any adverse events that may have occurred as part of the research procedures. We are proud to report that no patients have incurred adverse events as a result of participating in our specimen collection research protocols.

Institutional Renal Cell Carcinoma Clinical Database

The Stanford Renal Cell Carcinoma Database (RCCD), is a medical center database consisting of clinical, demographic, and outcomes data for all patients with RCC treated at Stanford from 2003 to the present. Participant data is entered into the RCCD through an automated process, and is then curated to ensure data quality. Variables include date of diagnosis, date of surgery, clinical staging, pathologic staging, pathologic features, dates and types of treatment received, response to treatment, patient performance status, adverse events, and date of death.

Specimen Database

The specimen database is specific to our RCC specimen acquisition efforts, and is designed to track all the parameters of the samples collected using the research protocols. This database is constructed using Research Electronic Data CAPture (REDCap, https://www.project-redcap.org), a HIPAA-compliant secure web application designed to support data capture for research studies, provide an intuitive interface for validated data entry, and audit trails for tracking data manipulation and export procedures.[20] Stanford maintains a version of REDCap that restricts access to users with active Stanford login credentials accessing REDCap from an on-campus computer or Stanford VPN, as well as project-specific user access to protect research information. REDCap is also approved for research for Veterans participating through the VA Palo Alto Health Care System. Within REDCap,

we have implemented data collection tools to store the pre-analytic variables associated with each specimen. These tools are organized into fields that denote particular aspects of the patient's treatment, as well as specific information about the samples that essentially tells the "story" for each sample we collect. (**Figure 3**) For example, one field contains all the information leading up to resection of the tumor, such as the type of procedure performed, laterality, how the patient was diagnosed, clinical stage, and RCC risk factors. The database also contains relevant pathologic data, including stage and grade, tumor size, and histologic subtype. We record all of the data pertaining to the procurement of the tissue, such as how the tissue was harvested, storage medium, and sample ischemia time. Finally, we are able to track which tissue was collected for which laboratory and research project. REDCap also can export data formatted for various statistical software packages (e.g. SAS and R) allowing for efficient analysis of the data as the study matures.

Future Directions

Analysis of biospecimens will be required to meet the increasing opportunities to advance our understanding of RCC biology. Current RCC research involves "team science" in the truest form, relying on clinicians, researchers, and research coordinators to succeed. As research tools increase in complexity, strategies to support these efforts with biospecimens and to collect biospecimens in novel ways must evolve in parallel. We intend to expand our internal RCC biospecimen and repository collaborations among the many laboratories studying RCC. We will continue to share standard operating procedures (SOPs) that have been optimized for specific assays. Further, we are working to share pre-analytic variables and storage parameters of residual biospecimens after the completion of the initial experiments. In doing so, we will encourage maximal use of the collected biospecimens, but also identify opportunities to build on existing research findings with future complementary studies. By mandating that laboratories share this information in a central location, we can effectively establish a more comprehensive picture of an individual tumor's biology by combining and examining the diverse array of information that each laboratory generates. We believe that this data will provide greater insight into the biology of RCC, and in turn fuel collaborations between researchers to answer more complex questions about RCC disease process.

We also hope to build collaborations outside of our institution, sharing SOPs, as well as granular details of available RCC specimens. The National Cancer Institute already supports on-line tools to share SOPs and research specimen information through the Biospecimen Research Database (https://brd.nci.nih.gov/brd/) and Biospecimen Pre-analytical Variables (BPV) Program (https://biospecimens.cancer.gov/programs/bpv/default.asp). These tools, or others created specifically for groups, will support collaborative studies essential to studying rare forms of RCC. We appreciate the opportunity to share our experience developing this infrastructure, and look forward to efforts within the kidney cancer research community to build biospecimen repositories to support the translational and basic research that will improve the care of patients with kidney cancer.

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↓

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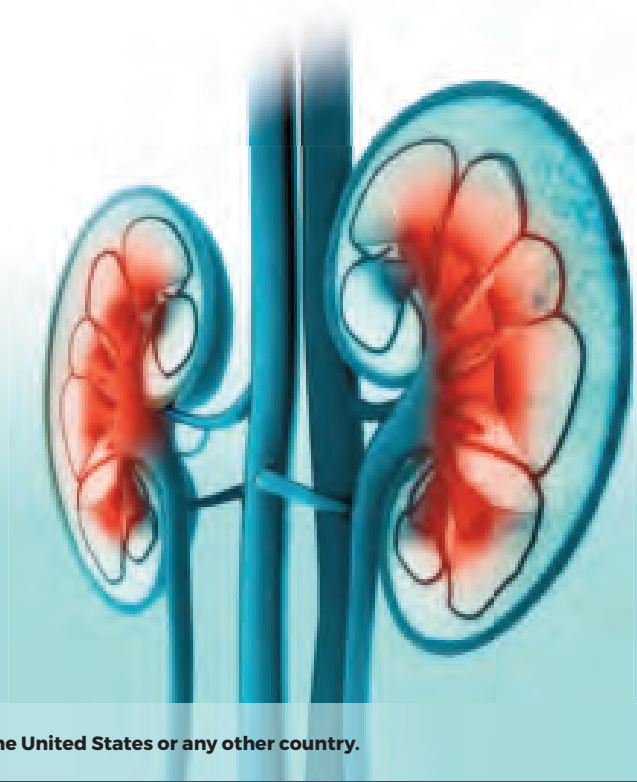

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GU ASCO 2019

Encapsulating Highlights Through the Lens of a Key Opinion Leader With Insights, Forecasts and Take-Home Messages

Nicholas J. Vogelzang, MD, FASCO, FACP, medical oncologist with Comprehensive Cancer Centers of Nevada (CCCN). He serves as Associate Chair of the Genitourinary Committee for US Oncology Research. The author and co-author of hundreds of peer-reviewed articles in the oncology literature, he serves as Vice Chair of GU Committee SWOG, a worldwide network of researchers that design and conduct cancer clinical trials. Dr Vogelzang is also Clinical Professor of Medicine at University of Nevada School of Medicine as well as Clinical Professor at UNLV School of Medicine, Las Vegas, Nevada.

This is GU ASCO 2.0, a fresh, intuitive, yet evidence-based analysis. In this wide ranging interview, Dr Vogelzang drills beyond the data to build a translational framework for interpreting results presented at GU ASCO as he highlights the potential impact of emerging results on clinical practice during this interview with the Kidney Cancer Journal.

Q: Comparing this year's meeting of GU ASCO to several years of similar scientific sessions, what impressions did you come away with this year? In your analysis last year for the Kidney Cancer Journal you did not see any major shift in the treatment paradigm. Was this year different?

Dr Vogelzang: Yes, I thought it was a very exciting time in contrast to earlier years. The fact that avelumab/axitinib and the pembrolizumab/axitinib studies were presented and that the nivolumab/ipilimumab (nivo-ipi) combination was updated made for a lot of hallway and backroom discussion. We have all been looking for a bit of advantage of one regimen over another and what we would do in the 'real world.' When my colleagues and I met at seminars with representatives from three major companies, Eisai, Merck and Pfizer, they expressed excitement as well.

Q: How would you characterize the obstacles that still need to be overcome in clinical trials?

Dr Vogelzang: The crux of the matter is that we do not have cross-trial comparisons. We have four dual agent trials all of which were superior to the standard agent sunitinib given on the 4/2 schedule—pembrolizumab/axitinib, avelumab/axitinib, atezolizumab/bevacizumab and nivo-ipi. If one compares them in a table format by patient characteristics, primary and secondary end points, there are multiple imbalances.

Q: If the comparisons are difficult to equate, what strikes you from a clinical standpoint as most dramatic?

Dr Vogelzang: The bottom line on this is that avelumab/axitinib and atezolizumab/bevacizumab did not hit (yet) the overall survival endpoint. They hit PFS which is by every account an FDA approvable endpoint. On the other hand, pembrolizumab/axitinib not only hit PFS but also hit an OS endpoint, which is wonderful since the RCC research community does not ordinarily achieve OS. Now, when you look at nivo-ipi, it initially hit overall survival in the intermediate and poor risk subgroups of patients. Data presented at GU ASCO provided some evidence for utilizing nivo-ipi in good risk patients as well, because of increased number of complete responses compared with sunitinib, and the durability of those complete responses. In his presentation and based on these updated results from CheckMate 214, Nizar Tannir recommended that nivo-ipi may be used for all patients with mRCC, regardless of risk classification. Dr Tannir indicated that OS was equivalent but that there were more CRs in the nivo-ipi group vs sunitinib. What is the upshot of the 2019 studies? It seems that pembrolizumab/axitinib and nivo/ipi are the top 2 regimens of choice because of their improvement in OS. Avelumab/axitinib and atezolizumab/bevacizumab are strong contenders because of their excellent tolerability and PFS advantage. If they show a survival advantage with future follow-up they will be considered equal to the other regimens.

Q: It seems that we have gone far beyond the earlier treatment algorithms that to a large degree dictated therapeutic choices. It's a far more complicated calculus now. Can you delve a bit further into the relative merits of PFS and OS with relation to patient subgroups and the benefit of these therapies based on prognostic risk factors? Isn't PFS considered a surrogate marker for OS?

Dr Vogelzang: Yes, PFS is considered a surrogate for OS and that's what is sort of ironic. When the bar gets raised as it has been lately, you start going beyond PFS per se to consider factors such as the overall survival advantage for nivo-ipi in pre-specified subgroups. In that context, and bringing in data from the other studies, it looks like pembrolizumab/axitinib had an OS advantage in all three subgroups—favorable, intermediate and poor risk. The intermediate risk group is the big category by percent and none of the three studies subdivided the intermediates into intermediate-favorable and intermediate-unfavorable risk. The Italian group Iacovelli et al (Clin Genito-

urinary Cancer 2018 Oct 16(5) 355-359) reporting on 846 patients, showed striking differences in the survival of intermediate-favorable patients (one risk factor =34 mos OS),real-intermediate (2 risk factors= 20 mos OS) and poor-intermediate (> 2 risk factors = 9 mos OS). This was first proposed by Sella et al (CGC 2017), and thus seems to be an important refinement of the MSKCC and IMDC risk groups. However, the studies did use retrospective analyses of sunitinib and pazopanib trials, not immunotherapy trials. Thus, if the studies are imbalanced in regards to these subgroups, differences in outcomes could be expected.

Q: In looking at the pivotal studies presented at GU ASCO, to what extent do various discrepancies in patient characteristics among the trials tend to skew the results and what's the impact, if any?

Dr Vogelzang: When you review the results of the three studies, we cannot really explain these differences because the studies did not subdivide the intermediate risk groups. All the studies were well balanced, large studies, but to some extent it depends on where the studies obtained the patients. In the US, patients generally present earlier than patients in Eastern Europe and Russia and may have fewer poor risk features. Also there is likely to be more third-line and fourth line treatments which may impact OS

Q.: So what was the impact of GU ASCO on your practice? When you returned to your office and the next metastatic RCC patient walks in the door, what's your plan?

Dr Vogelzang: At various roundtables held outside the symposia's agenda for attendees, I made the point and others tended to agree that nivo-ipi is readily available and has a survival advantage for all three of the risk groups—good, intermediate, and poor risk, based on CheckMate 214. If you then look at avelumab/axitinib which did not yet have that advantage and which is still pending FDA approval, we all started looking at the side effect profiles. Avelumab/axitinib, for example, had fewer side effects than nivo-ipi which in turn appeared to have fewer side effects than pembrolizumab/axitinib.

Q: But don't you need to tolerate the side effects to obtain benefit?

Dr Vogelzang: Yes, maybe, but for the good risk patients, I'm not sure we need to have side effects because patients do reasonably well with a TKI. Remember, sunitinib and pazopanib are still very good drugs for good-risk patients.

Q: If a community oncologist asked you for a summary of sorts, what take-home messages would you suggest? And what are the key factors to be mindful of as you define and refine your strategies?

Dr Vogelzang: For my good risk and favorable-intermediate patients I'm probably going to use the VEGF inhibitor axitinib upfront with either pembrolizumab or avelumab. A lot of it depends on what drugs are covered by what health plan. For the unfavorable-intermediate group and for the poor risk group I'm going to use nivo-ipi. So there is this refinement in my thinking going on. If you think about the biology of this disease, perhaps the patients with the bad genetics (BAP deletions) or more significant mutational burdens, will probably need a bigger immunological hit, therefore, nivo-ipi. Those patients with small deletions in 3p, and VEGF driven, will probably do extremely well with axitinib and a checkpoint inhibitor.

Q: A poster at GU ASCO examined the use of nivo-ipi after nivolumab alone. Is there likely to be an advantage in that subset?

Dr Vogelzang: There were definite responses there, and it suggests that the combo of nivo-ipi has some advantages over nivo alone. I am not sure how much of an advantage but there is some benefit there. However, toxicities are higher with nivo-ipi. Nevertheless, the duration of response may be better with the combination compared to nivo alone. That comparative study should be done.

Q: Let's return to the issue of prognostic factors and how to more effectively drill down and integrate them into decision making with all these combinations available. What do you foresee happening in this regard?

Dr Vogelzang: Ultimately we will get a prognostic signature. The prognostic signature will be, how good is good and how poor is poor? On this spectrum from very good to very poor we will need to position our thera-peutic agents. I always tell my colleagues, you have no idea who is going to walk in the door the next day. When you see these patients, they are 'disasters' from a clinical perspective. In these cases, it should probably be a de-cision to give these patients nivo-ipi. But you may not want to wait long enough to get the insurance approval. You may want to start them on a TKI immediately, just to put out the fire in these patients. This is where the cancer is just blowing up.

Q: Which TKI?

Dr Vogelzang: Based on what I've seen, I usually try to get axitinib or cabozantinib, but remember, axitinib by itself does not have first-line indication. I'll need to put in the order for axitinib/avelumab or axitinib/pembrolizumab and hopefully not wait too long to get the drugs approved. Every insurance company makes you wait three days for no good reason. So ultimately, the decision often comes down to mundane, nitty gritty details, like, how long is it going to take to get these drugs approved? What are the underlying immunological side effects? Are you comfortable giving nivo-ipi to someone with possibly underlying autoimmune disease? There's a certain granular aspect to the process of making these choices and I literally do not always know the obvious thing to do. For financially challenged people, the co-pays are important. I will write a prescription for one of the high-cost drugs and I'll tell the patient, "I hope you get it in two weeks." That may be fine for a good risk patient but in poor risk patients I don't want to wait two weeks where the average

survival is eight months. I want those patients to start on the drug tomorrow.

Q: Let's touch upon second-line therapy. What guidelines can you offer there?

Dr Vogelzang: In the second line we're looking at a lot of cabozantinib use. It's the go-to drug for a patient who progresses through nivo-ipi. In the last four months I have had three patients with no response to nivo-ipi. One of the patients is already dead—died in less than four months. We're not curing these poor-risk patients. If the patient rapidly progresses on nivo-ipi, I'll give them cabozantinib. And even cabozantinib, although a great drug, will have an uphill battle to delay cancer progression. Here's another case: one of my poor-risk patients is an architect but his disease progressed rapidly through nivo-ipi. When I put him on cabozantinib, he had a 3 cm neck node. It has decreased to about 1.5 cm. It's still there and feel it every time I see him. He has a big primary intact, lots of nodal disease and lung metastases. If cabozantinib fails, I will use lenvatinib/everolimus next. My current sequence tends to be nivo-ipi, second line cabozantinib, and third line lenvatinib/everolimus.

Q: Among the abstracts attracting interest was the TIVO-3 study involving tivozanib. Do you find this intriguing despite the troubled history of the drug in seeking FDA approval?

Dr Vogelzang: It's a wonderful drug. The latest results are positive but unfortunately the FDA has withheld approval because of the initial trial where there was inequality in survival due to differential use of second line therapy. It is ironic that it has been approved in Europe. Tivozanib is like other high-potency anti-VEGF agents, lenvatinib and axitinib and would be expected to combine well with immune check point inhibitors.

Q: You have shared your excitement about the new combinations and as we look toward future directions, what is the most pressing need to be addressed by studies before the next GU ASCO meeting?

Dr Vogelzang: It's an exciting time with improvements in PFS and OS but we still are not able the cure the vast majority of patients with metastatic RCC. The next steps are to compare these various regimens (likely in the cooperative groups), focus on the poor risk patients where progress can be quickly measured and work on 3 drug regimens such as nivo/ipi/cabozantinib or nivo/ipi/axitinib.

Selected Key Abstracts from the GU ASCO Kidney Cancer Meeting

[Editor's note: abstracts presented here are in abbreviated form. For the full abstracts, please visit the following link: https://meetinglibrary.asco.org/session/11665]

■ Thirty-month follow-up of the phase III CheckMate 214 trial of first-line nivolumab + ipilimumab (N+I) or sunitinib (S) in patients (pts) with advanced renal cell carcinoma (aRCC).

Nizar M. Tannir, Osvaldo Arén Frontera, Hans J. Hammers et al.

Background: N+I showed superior OS v S in ITT (IMDC any risk) and intermediate/poor-risk (I/P) pts with aRCC in CheckMate 214 at 17.5 mo min follow-up.

Methods: Pts with clear cell aRCC were randomized 1:1 to N3 mg/kg + I1 mg/kg Q3W×4 and then N3 mg/kg Q2W, or S 50 mg daily for 4 wk on, 2 wk off. Co-primary endpoints were OS, RECISTv1.1 ORR and PFS per IRRC in I/P pts. PFS and ORR were assessed by investigator (inv) at 30 mo.

Results: At 30 mo min follow-up, OS remains significantly improved in ITT and I/P pts with N+I v S; the HR for OS in favorable (fav) risk pts has improved for N+I v the previous analysis (1.22 [95% CI 0.73–2.04] v 1.45 [99.8% CI 0.51–4.12]). Per previous IRRC ORR (N+I, 42% [95% CI 37–47]; S, 27% [95% CI 22–31]), ORR per inv was higher with N+I v S in ITT and I/P pts. ORR CIs overlapped in fav pts, CR was doubled with N+I v S. Increasing PFS benefit with N+I v S is emerging in ITT and I/P pts; PFS CIs between arms remain overlapping in fav pts. 15% v 9% of N+I and S ITT pts remain on therapy, and 48% v 61% have received 2nd-line systemic therapy; 39% of S pts received subsequent immune-checkpoint inhibitor therapy. Among pts who were alive with CR, 50% v 10% remain on treatment with N+I (n = 56) v S (n = 10). 5 N+I and 7 S additional pts developed Gr 3–4 drug-related AEs; 1 N+I and 3 S additional pts had AEs leading to discontinuation. No new drug-related deaths occurred.

Conclusions: At 30 mo min follow-up, OS and ORR remain improved with N+I v S in ITT and I/P CheckMate 214 pts. No new safety signals emerged with longer follow-up. Clinical trial information: NCT02231749

■ Results of a phase II study of atezolizumab and bevacizumab in non-clear cell renal cell carcinoma (nccRCC) and clear cell renal cell carcinoma with sarcomatoid differentiation (sccRCC).

Rana R. McKay, Bradley Alexander McGregor, Kathryn Gray, et al

Background: The combination of atezolizumab and bevacizumab has demonstrated safety and efficacy in ccRCC. In this multicenter, phase II, open-label, single arm trial we evaluate the efficacy of atezolizumab and bevacizumab in patients with nccRCC and sccRCC with >20% sarcomatoid differentiation.

Methods: Eligible patients had an ECOG performance status of 0-2 and may have received prior therapy. Prior PD-1/PD-L1 therapy was not allowed. Patients underwent a mandatory baseline biopsy and subsequently received atezolizumab 120 mg and bevacizumab 15 mg/kg intravenously every 3 weeks. Patients remained on therapy until radiographic progression, unacceptable adverse events, or withdrawal. The primary end point was overall response rate (ORR) as determined by RECIST version 1.1.

Results: 65 patients were enrolled of whom 52 had ≥1 response assessment and were included in this analysis. 36 patients had nccRCC (papillary n=14, chromophobe n=8, unclassified RCC n=3, collecting duct n=3, trans-

location n=3, other n=5), and 16 patients had sccRCC. 17 patients received prior systemic therapy, 16 of whom had nccRCC. The ORR was 31% in the overall cohort. 10 patients (19%) developed grade 3 treatment-related adverse events (AEs), half of which were immune-related. There were no grade 4-5 AEs.
Conclusions: In this study, we show that therapy with atezolizumab and beva-cizumab was safe and demonstrated anti-tumor activity in nccRCC and sccRCC. Further analyses will report ORR by histologic subtype and PD-L1 expression status. Analysis of tissue and blood-based biomarkers of response are ongoing. Clinical trial information: NCT02724878

■ **Pembrolizumab (pembro) plus axitinib (axi) versus sunitinib as first-line therapy for locally advanced or metastatic renal cell carcinoma (mRCC): phase III KEYNOTE-426 study.**
Thomas Powles, Elizabeth R. Plimack, Viktor Stus, et al.
Background: A phase 1b study of pembro (anti–PD-1) plus axi (VEGFR-TKI) showed promising antitumor activity and manageable safety in patients (pts) with previously untreated mRCC. The global, open-label, phase 3 KEYNOTE-426 study assessed the efficacy and safety of pembro + axi vs sunitinib as first-line therapy for mRCC (NCT02853331).
Methods: Eligible pts with clear-cell mRCC, no previous systemic therapy for mRCC, and KPS ≥70% were randomized 1:1 to pembro 200 mg IV Q3W for a maximum of 35 cycles plus axi 5 mg orally BID or sunitinib 50 mg orally QD (4-wk on/2-wk off schedule). Treatment was given until PD, intolerable toxicity, or pt/investigator decision. Randomization was stratified by IMDC risk group and geographic region. Primary endpoints were OS and PFS (RECIST v1.1 by blinded, independent central review [BICR]). ORR was the key secondary endpoint. At the protocol-specified first interim analysis, the superiority thresholds were P = 0.0001 for OS, 0.0013 for PFS, and 0.025 for ORR (if OS and PFS were significant).
Results: 861 pts were randomized: 432 to pembro + axi, 429 to sunitinib. After a 12.8-mo median follow-up, 59.0% of pts in the pembro + axi arm and 43.1% in the sunitinib arm remained on treatment. Pembro + axi significantly improved OS (HR 0.53 [95% CI 0.38-0.74]; P< 0.0001; 12-mo rate 89.9% vs 78.3%), PFS (HR 0.69 [95% CI 0.57-0.84]; P = 0.0001; median 15.1 vs 11.1 mo), and ORR (59.3% vs 35.7%; P< 0.0001). Duration of response was prolonged with pembro + axi (median not reached vs 15.2 mo). The pembro + axi benefit was observed in all subgroups tested, including all IMDC risk and PD-L1 expression subgroups. Treatment-related AEs were grade 3-5 in 62.9% of pts in the pembro + axi arm vs 58.1% in the sunitinib arm and led to regimen discontinuation in 6.3% vs 10.1%.
Conclusions: Pembrolizumab + axitinib provided superior OS, PFS, and ORR compared with sunitinib and had manageable safety in pts with previously untreated, advanced or metastatic clear-cell RCC. These data suggest that pembrolizumab + axitinib should be a new standard of care for this population. Clinical trial information: NCT02853331

■ **Subgroup analysis from JAVELIN Renal 101: Outcomes for avelumab plus axitinib (A + Ax) versus sunitinib (S) in advanced renal cell carcinoma (aRCC).**
Toni K. Choueiri, Robert J. Motzer, Matthew T. Campbell, et al.
Background: In the ongoing phase 3 JAVELIN Renal 101 trial, progression-free survival (PFS) was longer (median, 13.8 vs 8.4 mo; hazard ratio, 0.69; p=0.0001) and the objective response rate (ORR) was higher (51% vs 26%) with A + Ax vs S in patients with previously untreated aRCC. Here we report outcomes from an analysis of several prespecified subgroups.
Methods: Patients were randomized 1:1 to receive A (10 mg/kg) IV every 2 weeks + Ax (5 mg) PO twice daily or S (50 mg) PO once daily for 4 wk (6-wk cycle). Primary and key secondary endpoints were PFS per independent review committee (IRC; RECIST v1.1) and OS in patients with PD-L1+ tumors (≥1% of immune cells) and in patients irrespective of PD-L1 expression; other secondary endpoints included OR per IRC (RECIST v1.1).
Results: A total of 886 patients were randomized; 560 (63%) had PD-L1+ tumors. At data cut-off (Jun 2018), median follow-up was 12.0 vs 11.5 mo for A + Ax vs S groups.
Conclusions: A + Ax demonstrated PFS and OR benefit across all prognostic risk groups and PD-L1 subgroups vs S in aRCC. Clinical trial information: NCT02684006

■ **A phase II study investigating the safety and efficacy of savolitinib and durvalumab in metastatic papillary renal cancer (CALYPSO).**
Thomas Powles, James M. G. Larkin, Poulam Patel, et al
Methods: This single arm phase I/II trial explored durvalumab and savolitinib at starting doses of 1500mg Q4W and 600mg OD respectively, with a 4wk savolitinib run-in. Treatment naïve or previously treated patients with metastatic PRC were included. Response rate (RR) (RECIST v1.1) was the primary endpoint. Progression free survival (PFS), tolerability (CTCAE v4) and overall survival were secondary endpoints.
Results: Dose escalation work identified a dose of durvalumab of 1500mg Q4W and savolitinib 600mg OD to take forward to phase II. Between Jan 2017 and Jul 2018, 42 patients were enrolled at this dose. 1 patient did not receive study treatment. The following analyses were performed on the remaining 41 patients. 12% of patients did not receive the combination (3 PD, 1 death, 1 PS deterioration). The median follow up was 8.9 months (95% CI: 6.9-10.9 months). IMDC good, intermediate and poor risk disease occurred in 29% (n=12), 63% (n=26), and 7% (n=3) patients respectively. Overall RR was 27% (11/41), while median PFS was 3.3 months (95% CI: 1.5-NR months). RR and median PFS in the previously untreated cohort (N=28) were 29% (8/28) and 12.0 months (95% CI: 1.5-NR months) respectively. Grade 3/4 toxicity occurred in 15 patients.
Conclusions: The combination of savolitinib and durvalumab appears safe and associated with clinical activity in PRC. Clinical trial information: NCT02819596. KCJ

A Novel Combination Therapy Takes an Innovative Approach by Targeting a Key Metabolic Pathway to Block RCC Growth

In this interview, a representative from the clinical development team of Calithera Biosciences discusses the potential impact of a novel drug combination undergoing study in a pivotal global randomized Phase 2 trial in renal cell carcinoma. Sam Whiting, MD, PhD, is Senior Vice President of Clinical Development. The new drug in development is teleglenastat (CB-839). One of the goals in the study is to demonstrate how targeting tumor metabolism pathways may take advantage of cancer-specific nutrient dependencies to block cancer growth. The interview was conducted by Robert A. Figlin, MD, Editor-in-Chief of the Kidney Cancer Journal.

Dr Figlin: Let's begin by examining some topics related to tumor metabolism and biology and how various factors could play a role in promoting cell growth and proliferation. Please describe the importance of metabolic pathways in kidney cancer and how your work relates to such mechanisms.

Dr Whiting: Metabolism is altered in cancer cells and a lot of oncologists know this from their training, that glucose metabolism in cancer typically is shunted toward production of lactic acid which is secreted from cells and shunted away from entry into the tricarboxylic acid (TCA) cycle, or Kreb's cycle. Called the Warburg Effect, this metabolic phenomenon has been known for almost a century. The problem has been how best to target the abnormal metabolism in tumor cells.

The unique thing about inhibition of glutaminase as targeted by teleglenastat (CB-839) is that alterations in glucose metabolism in tumor cells are linked to alterations in glutamine metabolism. And, in particular, as cells use less glucose to drive the TCA cycle and other biosynthetic pathways, they use more glutamine. What Calithera did was to develop an inhibitor of glutamine metabolism that would specifically block the conversion of glutamine to glutamate in the cancer cell and "starve" cancer cells of this necessary amino acid. This process is fundamentally important to cancer cells because of their altered metabolism.

So glutamine biology is important to cancer cells because of their inherent difference from healthy cells and that allows telaglenastat to have more of a metabolic impact on tumor cells compared to healthy cells, which is an important characteristic of the drug.

Dr Figlin: Help us understand some of the preclinical and Phase 1 results that have led to the CANTATA trial, which is looking at a combination with a tyrosine kinase inhibitor.

Dr Whiting: The first preclinical work that we performed with telaglenastat was biochemical studies in the laboratory to show that the drug hit its target in cancer cells, which is an enzyme called glutaminase, and hitting that target in cancer cells did what was expected, that is, shutting down glutamine metabolism in the cancer cell. We demonstrated in a large number of cancer cell lines, representing many different types of cancer, that telaglenastat shut down glutamine metabolism in the cancer cell. We also were able to track the repercussions of that blockade in a cancer cell, showing that downstream products of glutamine metabolism that cancer cells were relying upon were decreased or blocked as well. Those included molecules used for DNA synthesis, fatty acid synthesis, and to protect cancer cells from oxidative stress. All of these, we were able to show in the lab, were inhibited by telaglenastat but, importantly, it didn't have the same effect in normal tissues.

Dr Figlin: Can you differentiate aspects of tumor and normal cell metabolism that need to be considered? What effect does the drug have in these settings?

Dr Whiting: The reason for the drug not having the same effect on normal cells is that cancer cells, to put it a crude way, can be addicted to glutamine to feed pathways for which healthy cells predominantly use glucose. We had this metabolic inhibitory effect in cancer cells and we showed that the effect was not nearly as strong in healthy cells.

Then we went into tumor models in animals and showed that we can inhibit the growth of tumors in animals just as we could kill cancer cells in the lab. And again, looking in the animal, the impact of telaglenastat was predominantly seen in the cancer and not in healthy tissues. This took a few years of diligent work and, ultimately, led to the initial Phase 1 program where telaglenastat was tested in patients with cancer. That was a very thorough clinical program that looked at the drug in a significant number of patients with a variety of cancer types.

Dr Figlin: What led you to focus more specifically on RCC?

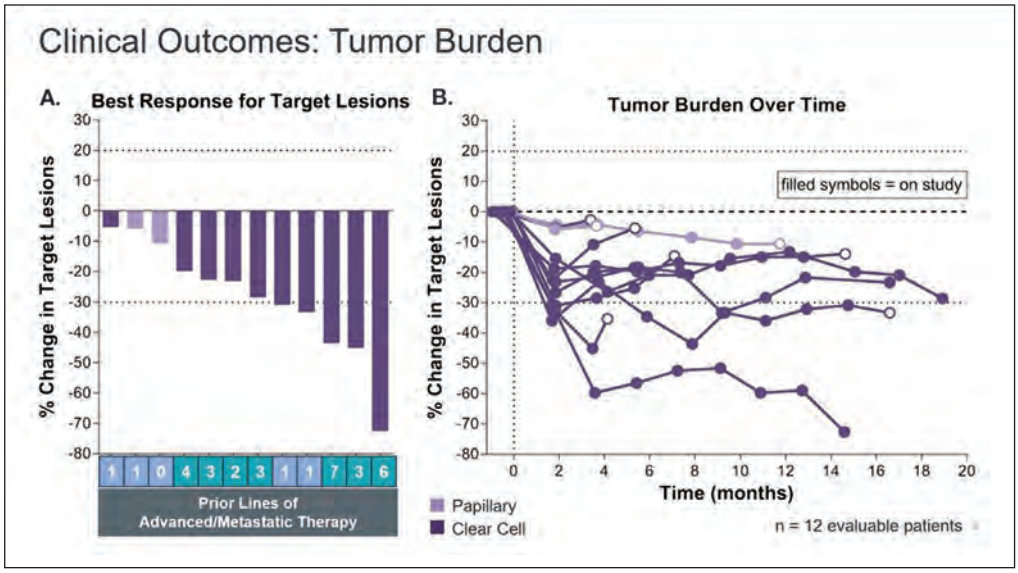

Figure. Panel A: Best response of target lesions per RECIST 1.1 including RCC subtype (papillary or clear cell) and prior lines of therapy. Panel B: Change in target lesions by serial tumor assessments over time per RECIST 1.1, including RCC subtype.

Dr Whiting: Kidney cancer was always the "poster child" - it was the principal focus of our development because kidney cancer is so classically altered from the standpoint of metabolism. Essentially, it is a great target for telaglenastat. The most common kidney cancer—clear cell renal cell carcinoma – is driven by a mutation in the VHL pathway. And 80% or more of clear cell RCC patients have a loss of this tumor suppressor pathway. As a result of that, it is known that they become more dependent on glutamine biology to support cancer cell growth and proliferation.

Consequently, from the beginning, kidney cancer was a very logical target, and in the Phase 1 program we tested telaglenastat in patients with kidney cancer. We actually saw activity in a few different subtypes of kidney cancer but found that maybe the most exciting was the clear cell type as expected. Very rapidly, actually, we looked at whether telaglenastat could be combined with other drugs that are standardly used to treat kidney cancer and if that combination could provide a synergistic or multiplicative benefit in patients.

We looked at two partner drugs early on—one was everolimus, an approved drug used in patients who are often in the third line or later of treatment. After that we looked at combining telaglenastat with cabozantinib, which is a newer approval in kidney cancer in 2016. And both of these combinations came out of the lab in the sense that we were able to show in cell lines that the two drugs together were able to hit both glucose and glutamine metabolism in a way that was synergistically damaging to cancer cells.

Dr Figlin: How encouraged were you by the response rates you observed?

Dr Whiting: That hypothesis was pursued in patients and we found that with both combinations, the everolimus combination and the cabozantinib combination, that there was encouraging activity in patients with advanced kidney cancer. The cabozantinib combination was particularly exciting to us because there was a response rate in which tumors shrank by a significant extent in 50% of patients with clear cell RCC. This was a small number of patients and needs to be confirmed in a larger trial that is now enrolling, but we knew that cabozantinib by itself had shown in published results a response rate of about 17%, and so 50% looked encouraging in that setting. We also had patients who were treated for a long period of time, so it looked like that benefit was durable.

We also had a toxicity profile for the two drugs together that looked to us and our investi-gators favorable because the combinations of telaglenastat with everolimus or cabozantinib looked similar to the standard drug alone – the tolerability was similar to everolimus or cabo-zantinib even when we added telaglenastat.

So that encouraging data led to a large, very rigorously designed clinical trial to formally test whether telaglenastat with cabozantinib, when used to treat patients with 2nd line or 3rd line clear cell RCC, was clearly a better treatment for patients than cabozantinib alone, which is a standard of care approach for these patients.

This is a trial that is randomized, so patients will get telaglenastat or placebo with the standard of care cabozantinib. It is blinded, so investigators and patients and the radiologists assessing outcomes do not know the treatment arm. It has a rigorous design in terms of assessing benefit and the company is hopeful that this will clearly show that this combination is active and helping patients with advanced RCC, leading to an approval for telaglenastat and making it available to patients with RCC.

Dr Figlin: Thank you for this discussion and sharing your insights. We look forward to further results from the clinical trial as they become available. KCJ

(continued from page 8)

sults showed that most patients present with metastatic disease, and prognosis remains extremely poor. Nephrectomy should be considered in all patients with acceptable surgical risk, including cytoreductive nephrectomy in carefully selected patients with metastatic disease.

Overweight and obesity during adolescence increases the risk of renal cell carcinoma. Landberg A, Fält A, Montgomery S, et al. *Int J Cancer*. 2019 Feb 20. doi: 10.1002/ijc.32147.
Summary: While overweight among adults has been linked with renal cell carcinoma (RCC) risk, little is known about the potential influence of overweight and obesity during adolescence. To ascertain if adolescent body mass index is associated with subsequent risk of RCC, we identified a cohort of 238,788 Swedish men who underwent mandatory military conscription assessment between 1969 and 1976 at a mean age of 18.5 years. At the time of conscription assessment, physical and psychological tests were performed including measurements of height and weight. Participants were followed through linkage to the Swedish Cancer Registry to identify incident diagnoses of RCC. The association between body mass index (BMI, kg/m2) at conscription assessment and subsequent RCC was evaluated using multivariable Cox regression. During a follow-up of up to 37 years, 266 men were diagnosed with RCC. We observed a trend for higher RCC risk with increasing BMI during adolescence, where one-unit increase in BMI conferred a 6% increased risk of RCC (95% CI 1.01-1.10) compared to normal weight men (BMI 18.5-<25), men with overweight (BMI 25-<30) or obesity (BMI ≥30) had hazard ratios for RCC of 1.76 and 2.87, respectively.
Conclusion: The link between overweight/obesity and RCC appears to be already established during late adolescence. Prevention of unhealthy weight gain during childhood and adolescence may thus be a target in efforts to decrease the burden of RCC in the adult population.

First-line nivolumab plus ipilimumab vs sunitinib for metastatic renal cell carcinoma: a cost-effectiveness analysis. Wan X, Zhang Y, Tan C, et al. *JAMA Oncol*. 2019 Feb 21. doi: 10.1001/jamaoncol.2018.7086.
Summary: Considering the high cost of nivolumab plus ipilimumab, there is a need to assess its value by considering both efficacy and cost. A Markov model was developed to compare the lifetime cost and effectiveness of nivolumab plus ipilimumab vs sunitinib in the first-line treatment of mRCC using outcomes data from the CheckMate 214 phase 3 randomized clinical trial, which included 1096 patients with mRCC (median age, 62 years) and compared nivolumab plus ipilimumab vs sunitinib as first-line treatment of mRCC. In the analysis, patients were modeled to receive sunitinib or nivolumab plus ipilimumab for 4 doses followed by nivolumab monotherapy. Life-years, quality-adjusted life-years (QALYs), and lifetime costs were estimated, at a willingness-to-pay threshold of $100,000 to $150,000 per QALY. Nivolumab plus ipilimumab provided an additional 0.96 QALYs, at a cost of $108,363 per QALY. Results were most sensitive to overall survival hazard ratio and mean patient weight (70 kg). Other variables, such as the cost of nivolumab plus ipilimumab (mean, $32,213.44; range, $25,770.75-$38,656.13), utility values for nivolumab plus ipilimumab (mean, 0.82), and proportion receiving nivolumab in sunitinib arm (mean, 0.27), had a moderate or minor influence on model results. Subgroup analyses demonstrated that nivolumab plus ipilimumab was most cost-effective for patients with programmed cell death 1 ligand 1 expression of at least 1% ($86,390 per QALY).
Conclusion: In this model, nivolumab plus ipilimumab was estimated to be cost-effective compared with sunitinib for intermediate- and poor-risk patients with mRCC at a willingness-to-pay threshold from $100,000 to $150,000 per QALY.

Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. Motzer RJ, Penkov K, Haanen J, et al. *N Engl J Med*. 2019 Feb 16. doi: 10.1056/NEJMoa1816047
Summary: This phase 3 trial involving previously untreated patients with advanced RCC compared avelumab plus axitinib with sunitinib. Patients were randomly assigned in a 1:1 ratio to receive avelumab (10 mg per kg) intravenously every 2 weeks plus axitinib (5 mg) orally twice daily or sunitinib (50 mg) orally once daily for 4 weeks (6-week cycle). Primary end points were progression-free survival and overall survival among patients with programmed death ligand 1 (PD-L1)-positive tumors. A key secondary end point was progression-free survival in the overall population; other end points included objective response and safety. A total of 886 patients were assigned to receive avelumab plus axitinib (442 patients) or sunitinib (444 patients). Among the 560 patients with PD-L1-positive tumors (63.2%), the median progression-free survival was 13.8 months with avelumab plus axitinib, as compared with 7.2 months with sunitinib (hazard ratio for disease progression or death, 0.61; in the overall population, the median progression-free survival was 13.8 months, as compared with 8.4 months (hazard ratio, 0.69; 95% CI, 0.56 to 0.84; P<0.001). Among the patients with PD-L1-positive tumors, the objective response rate was 55.2% with avelumab plus axitinib and 25.5% with sunitinib; at a median follow-up for overall survival of 11.6 months and 10.7 months in the two groups, 37 patients and 44 patients had died, respectively. Adverse events during treatment occurred in 99.5% of patients in the avelumab-plus-axitinib group and in 99.3% of patients in the sunitinib group; these events were grade 3 or higher in 71.2% and 71.5% of the patients in the respective groups.
Conclusion: Progression-free survival was significantly longer with avelumab plus axitinib than with sunitinib among patients who received these agents as first-line treatment for advanced renal-cell carcinoma.

Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. Rini BI, Plimack ER, Stus V, et al. *N Engl J Med*. 2019 Feb 16. doi: 10.1056/NEJMoa1816714.

Summary: The combination of pembrolizumab and axitinib showed antitumor activity in a phase 1b trial involving patients with previously untreated advanced renal-cell carcinoma. Whether pembrolizumab plus axitinib would result in better outcomes than sunitinib in such patients was unclear. This open-label, phase 3 trial randomly assigned 861 patients with previously untreated advanced clear-cell renal-cell carcinoma to receive pembrolizumab (200 mg) intravenously once every 3 weeks plus axitinib (5 mg) orally twice daily (432 patients) or sunitinib (50 mg) orally once daily for the first 4 weeks of each 6-week cycle (429 patients). Primary end points were overall survival and progression-free survival in the intention-to-treat population. The key secondary end point was the objective response rate. All reported results are from the protocol-specified first interim analysis. After a median follow-up of 12.8 months, the estimated percentage of patients who were alive at 12 months was 89.9% in the pembrolizumab-axitinib group and 78.3% in the sunitinib group. Median progression-free survival was 15.1 months in the pembrolizumab-axitinib group and 11.1 months in the sunitinib group. The objective response rate was 59.3% in the pembrolizumab-axitinib group and 35.7%in the sunitinib group (P<0.001). The benefit of pembrolizumab plus axitinib was observed across the International Metastatic Renal Cell Carcinoma Database Consortium risk groups (i.e., favorable, intermediate, and poor risk) and regardless of programmed death ligand 1 expression. Grade 3 or higher adverse events of any cause occurred in 75.8% of patients in the pembrolizumab-axitinib group and in 70.6% in the sunitinib group.

Conclusion: Among patients with previously untreated advanced RCC, treatment with pembrolizumab plus axitinib resulted in significantly longer overall survival and progression-free survival, as well as a higher objective response rate, than treatment with sunitinib. KCJ

MEDICAL INTELLIGENCE

(continued from page 9)

survey was disseminated in various patient communities using social media and was posted to the KCCure website in June 2018 after the presentation of the CARMENA trial. Patients were asked "The CARMENA trial presented recently at ASCO found that for kidney cancer patients diagnosed with metastatic disease, there is no overall survival benefit of having a nephrectomy prior to starting systemic therapy. Knowing that information, would you still want to have a nephrectomy at diagnosis if you were metastatic?"

Patients were also asked whether they had already had a nephrectomy and their stage at diagnosis and whether they were on systemic therapy. On the question of whether they would want nephrectomy 75.2% of the patients indicated they would still prefer nephrectomy. Of the patients with primary metastatic disease and the tumor in place treated with systemic therapy, 20.1% wanted their kidney tumor to be removed. There was no statistically significant difference between patients who had experience with systemic therapy and those who hadn't, and answers were also consistent regardless of gender and age. The conclusion of the authors: Overall survival should not be overestimated as the most important aim in an end-stage patient population. Patients might think differently about benefits, risks and value of surgical procedures than physicians. KCJ

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