Experience CABOMETYX®:

A TKI for aRCC patients after prior therapy

DEMONSTRATED EFFICACY

Clinical benefits observed across 3 key endpoints in a pivotal trial.[1]

SAFETY PROFILE

Risks associated with cabozantinib are not unexpected for a TKI targeting VEGF and can be managed with dose reductions.[2]

SIMPLE ONCE-DAILY DOSING

Available in 3 strengths should dose adjustment be required.[1]

HOME

OVERVIEW OF aRCC

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AE MANAGEMENT

IMPORTANT SAFETY INFORMATION

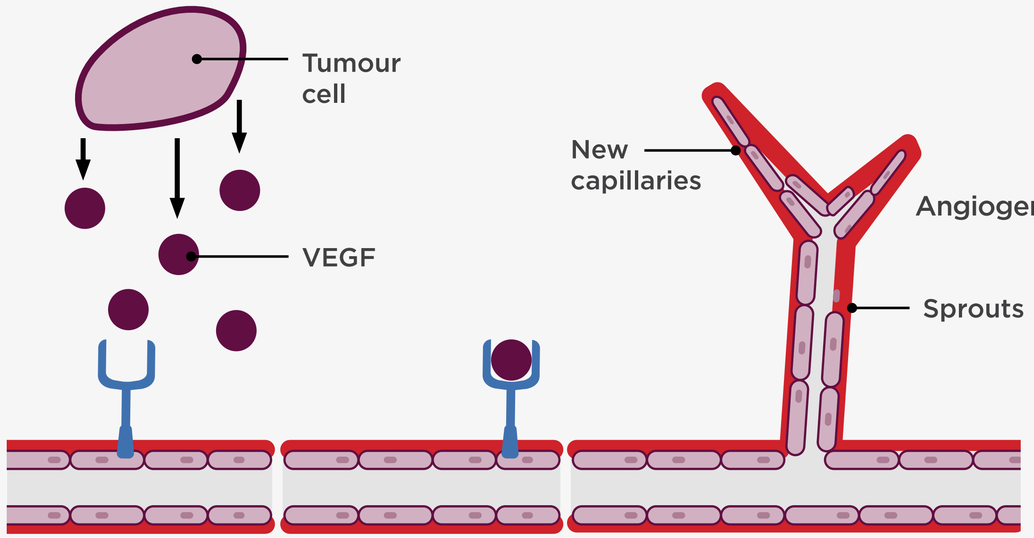
CABOMETYX® is indicated for the treatment of advanced renal cell carcinoma (RCC) in adult patients who have received prior therapy.

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

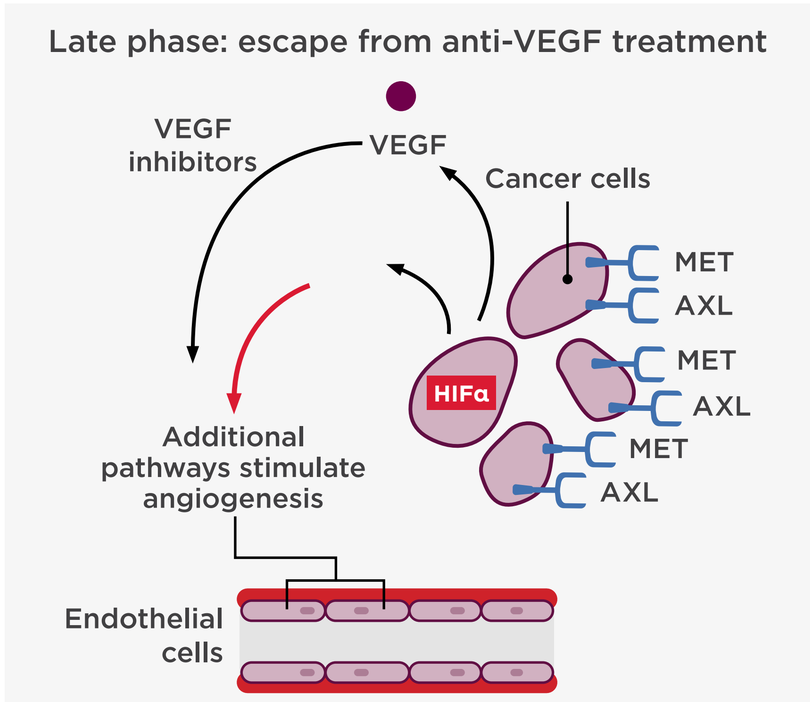
aRCC = advanced renal cell carcinoma; TKI = tyrosine kinase inhibitor; VEGF = vascular endothelial growth factor

OVERVIEW OF ADVANCED RENAL CELL CARCINOMA

VEGF is overexpressed in RCC resulting in angiogenesis and tumour progression[3]*



In patients with tumour progression, MET and AXL receptors were found to be upregulated[4-10]*



Increased expression of MET and AXL was associated with:[4-8,10,11]

- aggressive tumour phenotype
- poor patient outcomes
- development of resistance to VEGFR therapy

AXL = growth arrest-specific protein 6 receptor; HIF = hypoxia-inducible factor; MET = hepatocyte growth factor receptor; RCC = renal cell carcinoma; VEGF = vascular endothelial growth factor; VEGFR = VEGF receptor

* Clinical significance has not been established.

CABOMETYX®: METEOR PIVOTAL STUDY

In patients who received prior VEGF-targeted therapy, CABOMETYX® demonstrated significant clinical benefits across 3 endpoints[1]*

Progression-free survival

(in the first 375 patients, primary endpoint, per IRC)

HR=0.58† (95% CI, 0.45-0.74), *p*<0.0001

Median PFS:
CABOMETYX®
7.4 months

vs.

everolimus
3.8 months

Overall survival

(secondary endpoint, follow-up supplemental analysis)

HR=0.70‡ (95% CI, 0.58-0.85), *p*=0.0002§

Median OS:
CABOMETYX®
21.4 months

vs.

everolimus
17.1 months

Objective response rate

(PR only, secondary endpoint, by IRC)

CABOMETYX®
17%

vs.

everolimus
3%

p<0.0001

STUDY DESIGN | PATIENT DEMOGRAPHICS

aRCC = advanced renal cell carcinoma; CI = confidence interval; HR = hazard ratio; IRC = independent radiology committee review; MSKCC = Memorial Sloan Kettering Cancer Center; OS = overall survival; PFS = progression-free survival; PR = partial response; VEGF = vascular endothelial growth factor; VEGFR TKI = vascular endothelial growth factor receptor-targeting tyrosine kinase inhibitor

* METEOR: Randomized, open-label trial assessing CABOMETYX® vs. everolimus in aRCC patients with a clear cell component who previously received at least 1 prior VEGFR TKI. Patients were randomized 1:1 to CABOMETYX® 60 mg OD (n=330) or everolimus 10 mg OD (n=328), and tumour assessments were conducted Q8W for the first 12 months, then Q12W thereafter.

† Stratified log-rank test with prior VEGFR TKI (1 vs. 2+) and MSKCC prognostic criteria for previously treated patients (0 vs. 1 vs. 2 or 3) as stratification factors (per IVRS data).

‡ Cox proportional HR adjusted for stratification factors.

§ Stratification factors (based on IxRS) were prior VEGFR TKI: 1 vs. 2+ and MSKCC prognostic criteria (0 vs. 1 vs. 2 or 3).

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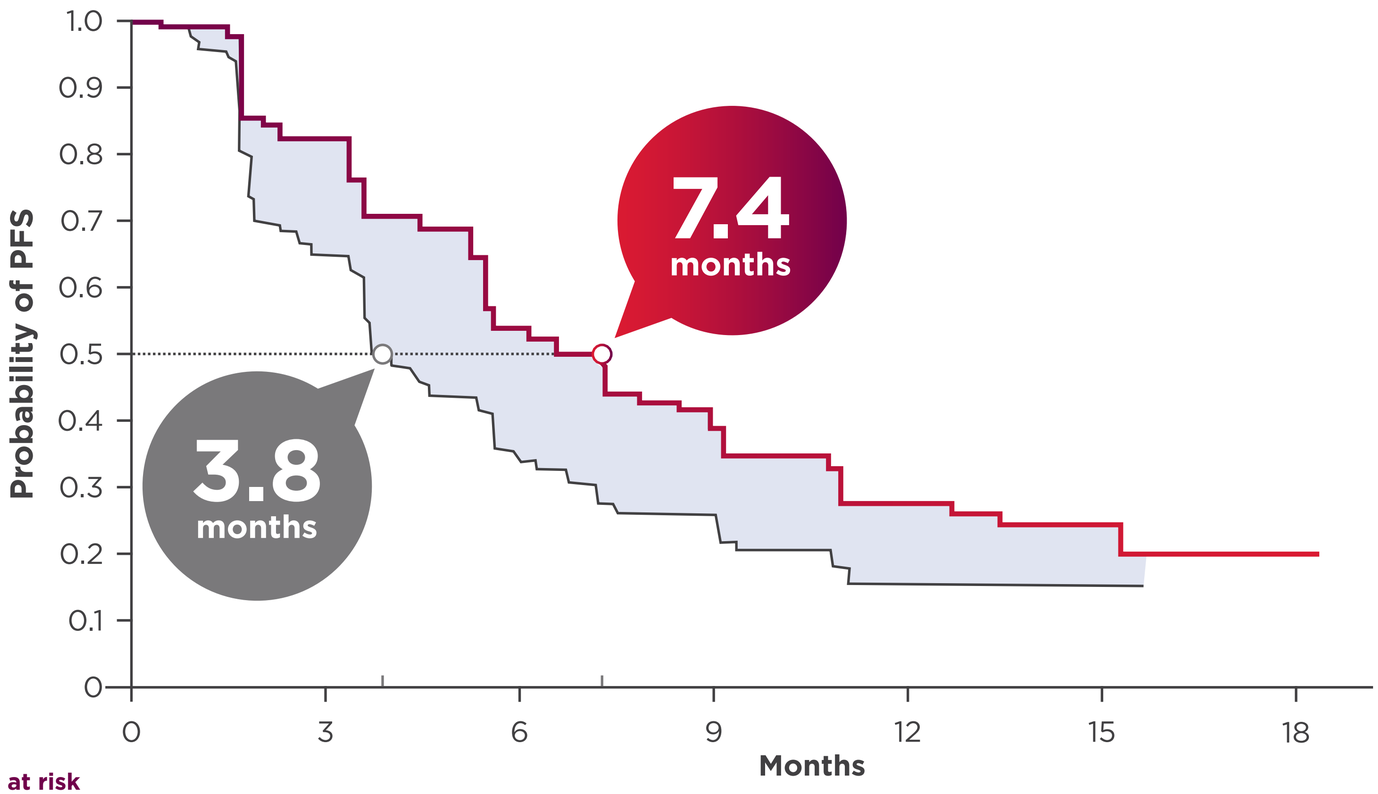
CABOMETYX® EXTENDED PROGRESSION-FREE SURVIVAL (PFS) VS. EVEROLIMUS

(HR=0.58* [95% CI, 0.45-0.74], *p*<0.0001; primary endpoint)[1]

Median PFS (first 375 randomized by IRC)



Patients at risk

CABOMETYX®	187	152	92	68	20	6	2
Everolimus	188	99	46	29	10	2	0

42% reduction in risk of progression or death

(Events: CABOMETYX® 121/187 vs. everolimus 126/188)[12]

HR=0.58* (95% CI, 0.45-0.74); *p*<0.0001

SUBGROUP ANALYSIS

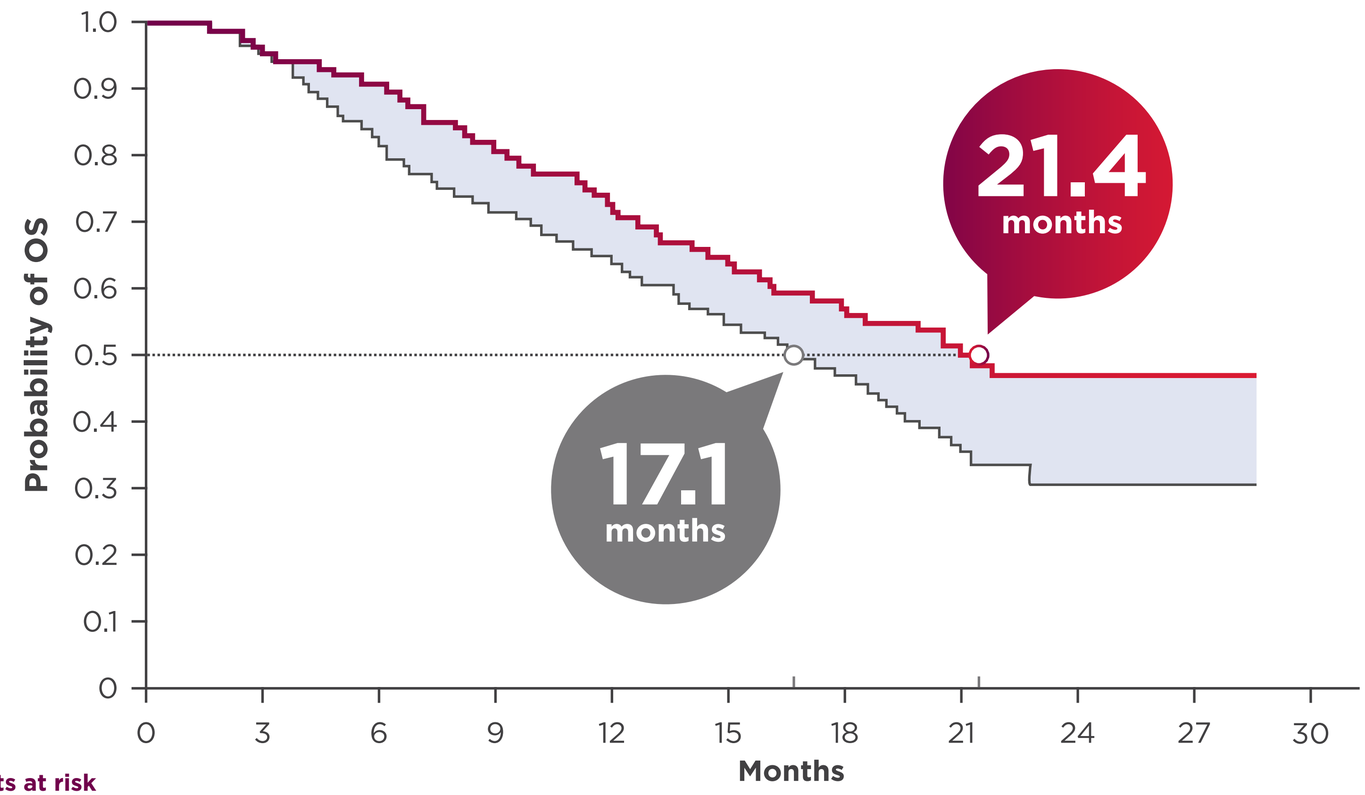
IRC = independent radiology committee review; MSKCC = Memorial Sloan Kettering Cancer Center; VEGFR TKI = vascular endothelial growth factor receptor-targeting tyrosine kinase inhibitor

* Stratified log-rank test with prior VEGFR TKI (1 vs. 2+) and MSKCC prognostic criteria for previously treated patients (0 vs. 1 vs. 2 or 3) as stratification factors (per IVRS data).

CABOMETYX® EXTENDED OVERALL SURVIVAL (OS) VS. EVEROLIMUS

(HR=0.70* [95% CI, 0.58-0.85], *p*=0.0002; secondary endpoint)[1†]

Median OS in the ITT population (follow-up supplemental analysis)



Patients at risk

CABOMETYX®	330	318	296	264	239	178	105	41	6	3	0
Everolimus	328	307	262	229	202	141	82	32	8	1	0

30% reduction in risk of death vs. everolimus

(Events: CABOMETYX® 198/330 vs. everolimus 232/328; Censored: CABOMETYX® 132/330 vs. everolimus 96/328)

HR=0.70* (95% CI, 0.58-0.85); *p*=0.0002†

SUBGROUP ANALYSIS

ITT = intent-to-treat; MSKCC = Memorial Sloan Kettering Cancer Center; VEGFR TKI = vascular endothelial growth factor receptor-targeting tyrosine kinase inhibitor

* Cox proportional HR adjusted for stratification factors.

† Stratification factors (based on IxRS) were prior VEGFR TKI: 1 vs. 2+ and MSKCC prognostic criteria (0 vs. 1 vs. 2 or 3).

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CABOMETYX®: SUBGROUP ANALYSES

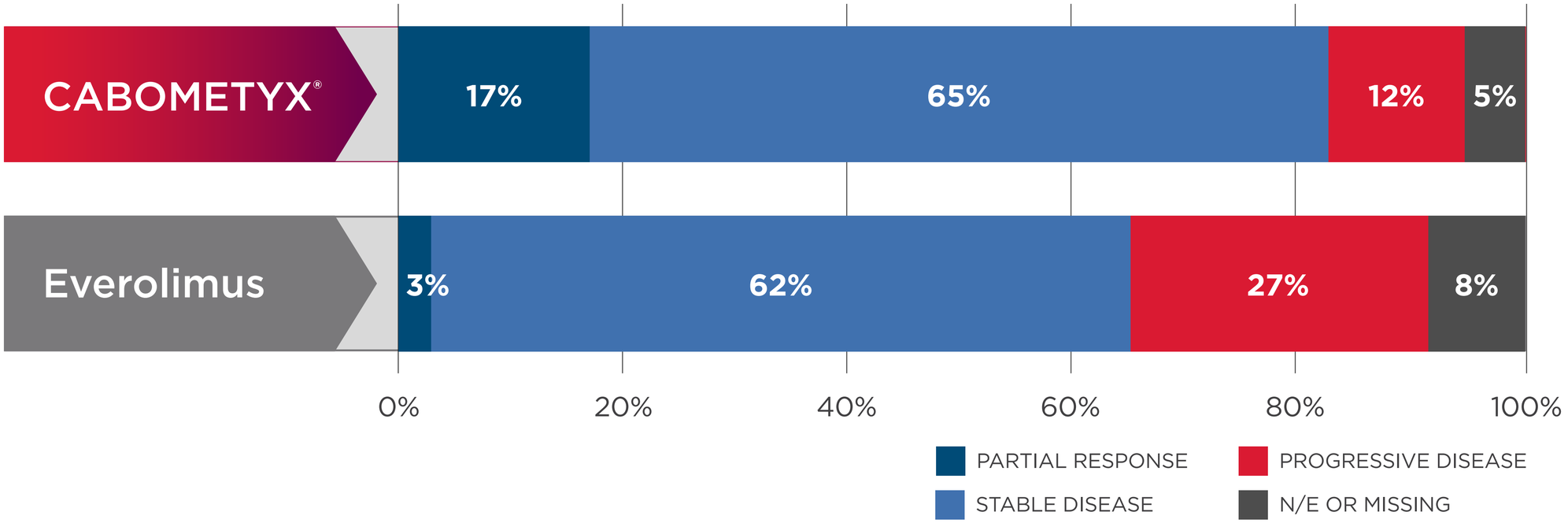
Exploratory analyses of PFS and OS showed consistent results in favour of CABOMETYX® across different patient subgroups (ITT population)[1,4]

	OS			PFS	
	Patients CABOMETYX®/ everolimus	Events CABOMETYX®/ everolimus	HR (95% CI)	Events CABOMETYX®/ everolimus	HR (95% CI)
Overall	330/328	140/180	0.66 (0.53-0.83)	180/214	0.51 (0.41-0.62)
Age					
<65 years	196/198	86/107	0.72 (0.54-0.95)	109/133	0.53 (0.41-0.68)
≥65 years	134/130	54/73	0.62 (0.44-0.88)	71/81	0.50 (0.36-0.69)
MSKCC risk group					
Favourable	150/150	48/66	0.66 (0.46-0.96)	79/92	0.51 (0.38-0.69)
Intermediate	139/135	64/79	0.67 (0.48-0.94)	74/89	0.47 (0.35-0.65)
Poor	41/43	28/35	0.65 (0.39-1.07)	27/33	0.70 (0.42-1.16)
ECOG status					
0	226/216	81/105	0.65 (0.49-0.87)	114/137	0.46 (0.36-0.59)
1	104/112	59/75	0.72 (0.51-1.02)	66/77	0.64 (0.46-0.90)
Previous VEGFR TKIs					
1	235/229	98/130	0.65 (0.50-0.85)	131/155	0.52 (0.41-0.66)
≥2	95/99	42/50	0.73 (0.48-1.10)	49/59	0.51 (0.35-0.74)
Duration of 1st VEGFR TKI					
≤6 months	88/102	42/65	0.69 (0.47-1.01)	56/70	0.62 (0.44-0.89)
>6 months	242/224	98/114	0.69 (0.52-0.90)	124/142	0.48 (0.38-0.62)
Bone metastases					
No	253/263	105/137	0.71 (0.55-0.91)	140/169	0.57 (0.45-0.71)
Yes	77/65	35/43	0.54 (0.34-0.84)	40/45	0.33 (0.21-0.51)
Visceral metastases					
No	89/83	32/40	0.70 (0.44-1.12)	44/47	0.64 (0.42-0.97)
Yes	241/245	108/140	0.66 (0.52-0.85)	136/167	0.48 (0.38-0.60)

ECOG = Eastern Cooperative Oncology Group; ITT = intent-to-treat; MSKCC = Memorial Sloan Kettering Cancer Center; OS = overall survival; PFS = progression-free survival; VEGFR TKI = vascular endothelial growth factor receptor-targeting tyrosine kinase inhibitor

CABOMETYX®: OTHER ORR FINDINGS VS. EVEROLIMUS (SUPPORTIVE ANALYSES)[1]

82% of CABOMETYX® patients had partial response or stable disease (best responses by IRC) vs. 65% of everolimus patients.

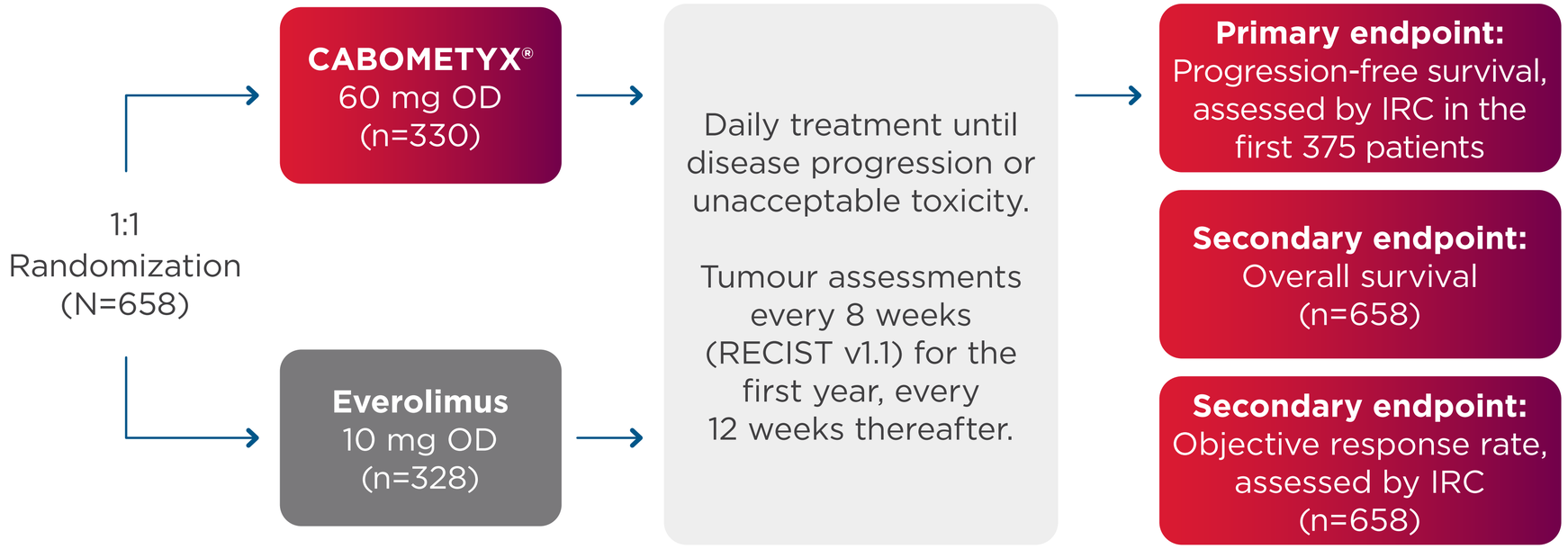


Median time to first response was **1.91 months with CABOMETYX®** vs. 2.14 months with everolimus.

IRC = independent radiology committee review; N/E = not evaluable; ORR = objective response rate

METEOR STUDY: A PIVOTAL PHASE 3 TRIAL

A randomized, open-label trial that compared the efficacy and safety of CABOMETYX® vs. everolimus in patients with aRCC (clear cell) who progressed on VEGF-targeted therapy[1,4]



Patients could have received any number of other prior therapies, including cytokines, and antibodies targeting VEGF, PD-1 or its ligands.

The majority of patients (71%) received only one prior VEGFR TKI.

aRCC = advanced renal cell carcinoma; IRC = independent radiology committee review; PD-1 = programmed death 1; RECIST = Response Evaluation Criteria in Solid Tumors; VEGF = vascular endothelial growth factor; VEGFR TKI = vascular endothelial growth factor receptor-targeting tyrosine kinase inhibitor

METEOR STUDY: A DIVERSE SET OF BASELINE CHARACTERISTICS

Select demographics and baseline characteristics[1,4]

	CABOMETYX® (n=330)	Everolimus (n=328)
Prior VEGFR TKIs		
1	71%	70%
≥2	29%	30%
Previous systemic therapy (any line)		
Sunitinib	64%	62%
Pazopanib	44%	41%
Axitinib	16%	17%
Sorafenib	6%	9%
Interleukin-2	6%	9%
Interferon-α	6%	7%
Nivolumab*	5%	4%
Bevacizumab	2%	3%
ECOG performance status		
0	68%	66%
1	32%	34%
MSKCC prognostic risk category		
Favourable	45%	46%
Intermediate	42%	41%
Poor	12%	13%
Metastatic site per IRC		
Lung	62%	65%
Lymph node	62%	61%
Liver	27%	31%
Bone	23%	20%
Brain	<1%	<1%
Other	7%	6%

ECOG = Eastern Cooperative Oncology Group; IRC = independent radiology committee review; MSKCC = Memorial Sloan Kettering Cancer Center; VEGFR TKI = vascular endothelial growth factor receptor-targeting tyrosine kinase inhibitor

* One additional patient in the CABOMETYX® group received prior atezolizumab.

CABOMETYX®: REAL WORLD EVIDENCE STUDY

CABOSEQ was a retrospective, observational cohort study using the IMDC.

Patient Population	1L Setting		2L Setting
Mean age: 60.77 years Sex: 75.1% male Mean KPS score: 85.24% IMDC risk Favourable: 5.3% Intermediate: 58.0% Poor: 36.7%	**ipilimumab** **+** **nivolumab**	→	**CABOMETYX®** **vs.** **sunitinib**

The emulated trial estimated the comparative effectiveness of second-line CABOMETYX® vs. sunitinib, in metastatic RCC patients who progressed on first-line ipilimumab + nivolumab.

- A protocol for a hypothetical target trial was specified, then emulated using observational data from the IMDC database.
- Overall survival (OS) and time to treatment failure curves were estimated using the Kaplan-Meier product-limit method, and a proportional hazard ratio was estimated using Cox regression.
- Objective response rate (ORR) and cumulative incidence were estimated and compared using the risk difference and risk ratio.
- Multiple imputation was used for missing values and inverse probability of treatment weighting was used to adjust for confounders. OS was adjusted for by IMDC risk factors at second-line initiation.

This Real World Evidence dataset demonstrated that CABOMETYX® can be a treatment option for aRCC patients after the first-line therapies, irrespective of whether the first-line regimen included a VEGF targeted therapy.

IMDC = International Metastatic RCC Data Consortium; KPS = Karnofsky Performance Status

CABOMETYX® HAS A PROVEN SAFETY PROFILE

CABOMETYX® was generally well tolerated in patients with aRCC.

Most common adverse reactions in ≥25% of CABOMETYX® patients previously treated with a TKI[1]

	CABOMETYX® (n=331)*		Everolimus (n=322)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Diarrhea	74%	11%	28%	2%
Fatigue	56%	9%	47%	7%
Nausea	50%	4%	28%	<1%
Decreased appetite	46%	3%	34%	<1%
PPES	42%	8%	6%	<1%
Hypertension†	39%	16%	8%	3%
Vomiting	32%	2%	14%	<1%
Weight decreased	31%	2%	12%	0%
Constipation	25%	<1%	19%	<1%

10% of patients in the METEOR study discontinued CABOMETYX® due to adverse events.[1]

Risks associated with cabozantinib are not unexpected for a TKI-targeting VEGF and can be managed with dose reductions.[2]

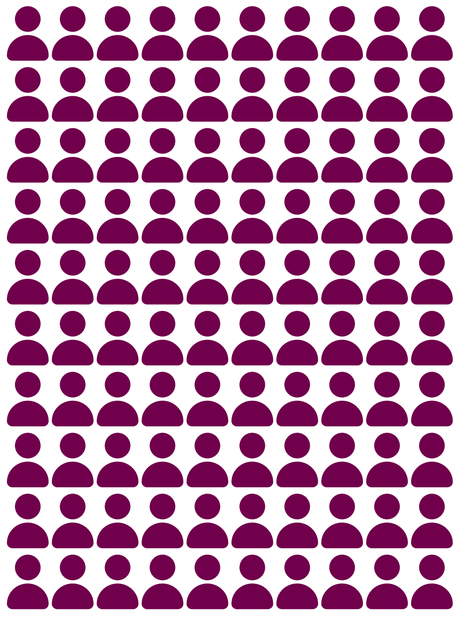
aRCC = advanced renal cell carcinoma; PPES = palmar-plantar erythrodysesthesia syndrome; TKI = tyrosine kinase inhibitor; VEGF = vascular endothelial growth factor
*One subject randomized to everolimus received CABOMETYX®.
†Includes hypertension, blood pressure increased, hypertensive crisis, blood pressure fluctuation.

ADVERSE EVENTS WERE ADDRESSED WITH DOSE REDUCTIONS, INTERRUPTIONS, OR DISCONTINUATIONS, IF NEEDED

Dose reductions | Dose interruptions and discontinuations

CABOMETYX® safety population in the METEOR study (n=331)[1]

100%
of patients received **60 mg** dose



60%
of patients had a first-level dose reduction due to AE (40 mg)

55 days – median time to first dose reduction

20%
of patients had a second-level dose reduction due to AE (20 mg)

Dose reductions[1]

Most common AEs leading to dose reduction: diarrhea (16%), PPES (11%), fatigue (10%) and hypertension (8.0%).[1]

AE = adverse event; PPES = palmar-plantar erythrodysesthesia syndrome

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ADVERSE EVENTS WERE ADDRESSED WITH DOSE REDUCTIONS, INTERRUPTIONS, OR DISCONTINUATIONS, IF NEEDED

Dose reductions | **Dose interruptions and discontinuations**

CABOMETYX® safety population in the METEOR study (n=331)[1]

Dose interruptions were required in 70% of patients.*

- Median time to first dose interruption was **38 days**.
- Most common AEs leading to dose interruptions: diarrhea (22%), PPES (14%) and fatigue (12%).
- Treatment was discontinued if interruption lasted >6 weeks.

Permanent treatment discontinuation was required in 10% of patients.

- Most common AEs leading to permanent discontinuation: decreased appetite (2%) and fatigue (1%).

AE = adverse event; PPES = palmar-plantar erythrodysesthesia syndrome
* Treatment interruption was allowed at the discretion of the investigator. CABOMETYX® was discontinued if interruption lasted more than 6 weeks.

DOSAGE MODIFICATIONS FOR ADVERSE REACTIONS[1]

Management of suspected adverse drug reactions may require temporary treatment interruption and/or dose reduction, or permanent discontinuation of CABOMETYX® therapy.

Dose modifications for coadministration with strong CYP3A4 inhibitors

Reduce the daily CABOMETYX® dose by 20 mg. Resume the dose that was used prior to initiating the strong CYP3A4 inhibitor 2 to 3 days after discontinuation of the strong inhibitor.

Dose modifications for coadministration with strong CYP3A4 inducers

Increase the daily CABOMETYX® dose by 20 mg as tolerated. Resume the dose that was used prior to initiating the strong CYP3A4 inducer 2 to 3 days after discontinuation of the strong inducer. Do not exceed a daily dose of 80 mg.

Dose modifications for patients with hepatic impairment

Reduce the starting dose of CABOMETYX® as monotherapy to 40 mg once daily in patients with moderate hepatic impairment. Patients with mild or moderate hepatic impairment should be closely monitored.

CABOMETYX® is not recommended for use in patients with severe hepatic impairment.

CYP3A4 = cytochrome P450 3A4

GUIDANCE FOR CABOMETYX® USE[1]

Assess baseline comorbidities and treat accordingly

Educate patient

Initiate CABOMETYX® at recommended dose (60 mg once daily).

Continue treatment until patient no longer experiences clinical benefit or experiences unacceptable toxicity.

Ongoing monitoring

Manage AEs with supportive care, dose reductions or treatment interruptions.

Dose interruptions are recommended for management of CTCAE grade 3 or greater toxicities or intolerable grade 2 toxicities.

Most CABOMETYX® AEs occur early in the course of treatment

Evaluate the patient closely during the first 8 weeks of treatment to determine the need for dose modifications.

Stop treatment with CABOMETYX® at least 28 days prior to scheduled surgery.

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events

CABOMETYX® OFFERS THE SIMPLICITY OF A ONCE-DAILY ORAL TREATMENT

CABOMETYX® is available in 3 strengths should dose adjustments be required[1]

Recommended dose  **60 mg daily**

IF NECESSARY

First reduction  **40 mg daily**

IF NECESSARY

Second reduction  **20 mg daily**

Evaluate patients closely during the first 8 weeks to determine if dose modifications are necessary.[1]

SPECIAL POPULATIONS

DOSE ADJUSTMENTS FOR AE MANAGEMENT

Refer to Product Monograph at health-products.canada.ca/dpd-bdpp/ for complete dosing information.

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CABOMETYX® DOSING IN SPECIAL POPULATIONS[1]

Start CABOMETYX® at the recommended 60 mg QD

Reduce starting dose to 40 mg QD

Elderly patients ≥65 years	Mild/moderate renal impairment (use with caution)	Mild/moderate hepatic impairment (monitor patients closely)

Not recommended/incompatible

Severe renal impairment	Severe hepatic impairment	Pediatrics
Reproduction/ Fertility (males and females)	Pregnancy	Breastfeeding

Refer to Product Monograph at health-products.canada.ca/dpd-bdpp/ for complete dosing information.

CABOMETYX® DOSING FOR ADVERSE EVENT MANAGEMENT[1]

No dose adjustment

Grade 1 and 2 AEs that are tolerable and easily managed.

Withhold CABOMETYX®

Interrupt CABOMETYX® for management of CTCAE grade 3 or greater toxicities or intolerable grade 2 toxicities.

Reduce CABOMETYX® dose

Reduce CABOMETYX® dose for AE that, if persistent, could become serious or intolerable.

When dose reduction is necessary, reduce to 40 mg daily, then to 20 mg daily.

Permanently discontinue CABOMETYX®

For any of the following:

- Development of unmanageable fistula or GI perforation
- Severe hemorrhage
- Arterial or venous thromboembolic event that requires medical intervention (e.g., myocardial infarction, cerebral infarction)
- Hypertensive crisis or severe hypertension despite optimal medical management
- Nephrotic syndrome
- Posterior reversible encephalopathy syndrome

Refer to Product Monograph at health-products.canada.ca/dpd-bdpp/ for complete dosing information.

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; GI = gastrointestinal

DIARRHEA MANAGEMENT

Diarrhea may occur early in the course of treatment with CABOMETYX®. Monitor patients closely during the first 8 weeks of therapy.[1]

Questions you may want to consider when assessing baseline signs and symptoms:[13]

- How many bowel movements do you have daily?
- Are they loose or watery?
- Is there a lot? A little?
- Is this typical or has it changed recently?

Considerations for patient counselling[13]

Advise patients to:

- Stay well hydrated and drink a variety of fluids daily to prevent dehydration
- Eat small, frequent meals, limit high-fibre foods, and remove skins from fruits and vegetables
- Avoid spicy, deep-fried, greasy foods

DIARRHEA GRADING

CTCAE v5.0 GRADES FOR DIARRHEA[14]

Grade 1	• Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline
Grade 2	• Increase of 4-6 stools per day over baseline • Moderate increase in ostomy output compared to baseline • Limiting instrumental ADL
Grade 3	• Increase of ≥ 7 stools per day over baseline • Incontinence • Hospitalization indicated • Severe increase in ostomy output compared to baseline • Limiting self-care ADL
Grade 4	• Life-threatening consequences • Urgent intervention indicated

ADL = activities of daily living; CTCAE = Common Terminology Criteria for Adverse Events

FATIGUE MANAGEMENT

Questions you may want to consider when assessing baseline signs and symptoms:[13]

- What percent of your daily routine is spent sedentary (i.e., sitting or sleeping)?
- Is conducting your usual activities making you more tired than normal?
- Do you consider yourself to be anxious or depressed?
- Do you feel that you get enough good quality sleep?

Considerations for patient counselling[13]

- Educate patients about fatigue, how to monitor it, and how to use energy-conserving and distraction strategies (e.g., setting priorities, pacing themselves)
- Advise patients to manage their activity levels (e.g., modify work schedule, get support for day-to-day activities)
- Educate patients on sleep hygiene (e.g., establishing a regular sleep pattern, avoiding screen time in the bedroom, etc.)

FATIGUE GRADING

CTCAE v5.0 GRADES FOR FATIGUE[14]

Grade 1	• Fatigue relieved by rest
Grade 2	• Fatigue not relieved by rest; limiting instrumental ADL
Grade 3	• Fatigue not relieved by rest; limiting self-care ADL

ADL = activities of daily living; CTCAE = Common Terminology Criteria for Adverse Events

HYPERTENSION MANAGEMENT

Hypertension may occur early in the course of treatment with CABOMETYX®. Monitor patients closely during the first 8 weeks of therapy.[1]

Questions you may want to consider when assessing baseline signs and symptoms:

- What is your normal blood pressure?
- Do you have a history of high blood pressure?
- Are you currently being treated for high blood pressure?
- Is your blood pressure stable and well controlled?
- Do you have any history of heart disease?

Considerations for patient counselling[15]

Advise patients to:

- Abstain from or reduce alcohol consumption
- Stop smoking
- Try to exercise daily
- Eat a healthy diet (limit sodium; select low-fat, whole-grain foods rich in dietary fibre)

HYPERTENSION GRADING

CTCAE v5.0 GRADES FOR HYPERTENSION[14]

Grade 1	• Systolic BP 120-139 mm Hg or diastolic BP 80-89 mm Hg
Grade 2	• Systolic BP 140-159 mm Hg or diastolic BP 90-99 mm Hg if previously within normal limits; change in baseline medical intervention indicated; recurrent or persistent (≥24 h); symptomatic increase by >20 mm Hg (diastolic) or to >140/90 mm Hg; monotherapy indicated initiated
Grade 3	• Systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg; medical intervention indicated; more than one drug or more intensive therapy than previously used indicated
Grade 4	• Life-threatening consequences • Urgent intervention indicated

BP = blood pressure; CTCAE = Common Terminology Criteria for Adverse Events

PALMAR-PLANTAR ERYTHRODYSESTHESIA SYNDROME (PPES) MANAGEMENT

PPES may occur early in the course of treatment with CABOMETYX®. Monitor patients closely during the first 8 weeks of therapy.[1]

Questions you may want to consider when assessing baseline signs and symptoms:[13]

- Have you ever had PPES/ hand-foot syndrome?
- Do you moisturize your hands and feet daily?
- Do you suffer from any ongoing skin complaints, e.g., lesions, eczema, very dry skin?

Considerations for patient counselling

- Inform patients about the visible signs of PPES
- Educate patients on prophylactic skin care techniques and implement a proactive skin care regimen
- Advise patients to contact their healthcare team if symptoms are severe

PPES GRADING

CTCAE v5.0 GRADES FOR PPES[14]

Grade 1	• Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis)
Grade 2	• Skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting instrumental ADL
Grade 3	• Severe skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting self-care ADL

ADL = activities of daily living; CTCAE = Common Terminology Criteria for Adverse Events; PPES = palmar-plantar erythrodysesthesia syndrome

NAUSEA AND VOMITING MANAGEMENT

Nausea and vomiting may occur early in the course of treatment with CABOMETYX®. Monitor patients closely during the first 8 weeks of therapy.[1]

Questions you may want to consider when assessing baseline signs and symptoms:[13]

- Do you typically suffer from any queasiness or nausea?
- How many times per day do you vomit?
- Is this triggered by any particular events?
- Does nausea or vomiting affect your eating habits?
- Do you consider vomiting to be a particularly distressful event?

Considerations for patient counselling[13]

Advise patients to:

- Aim to drink 8-10 glasses of fluids every day
- Eat small, bland, easy-to-digest foods, such as toast, crackers, and dry cereal
- Maintain oral hygiene

NAUSEA AND VOMITING GRADING

CTCAE v5.0 GRADES FOR NAUSEA[14]

Grade 1	• Loss of appetite without alteration in eating habits
Grade 2	• Oral intake decreased without significant weight loss, dehydration or malnutrition
Grade 3	• Inadequate oral caloric or fluid intake; tube feeding, total parenteral nutrition or hospitalization indicated

CTCAE v5.0 GRADES FOR VOMITING[14]

Grade 1	• Intervention not indicated
Grade 2	• Outpatient IV hydration; medical intervention indicated
Grade 3	• Tube feeding, total parenteral nutrition or hospitalization indicated
Grade 4	• Life-threatening consequences

CTCAE = Common Terminology Criteria for Adverse Events

CONSTIPATION MANAGEMENT

Constipation may occur early in the course of treatment with CABOMETYX®. Monitor patients closely during the first 8 weeks of therapy.[1]

Questions you may want to consider when assessing baseline signs and symptoms:[13]

- How many bowel movements do you have daily?
- Is this typical or has it changed recently?
- Describe your typical eating and drinking habits.
- How active are you? (% of day spent in bed or chair)

Considerations for patient counselling[13]

Educate patients regarding:

- The importance of regular physical activity (according to ability) and dietary measures to control constipation (i.e., high-fibre foods)
- Availability of dietitian consultation to modify diet, if necessary
- Importance of recording bowel movements

CONSTIPATION GRADING

CTCAE v5.0 GRADES FOR CONSTIPATION[14]

Grade 1	• Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification or enema
Grade 2	• Persistent symptoms with regular use of laxatives or enemas; limiting instrumental ADL
Grade 3	• Obstipation with manual evacuation indicated; limiting self-care ADL
Grade 4	• Life-threatening consequences; urgent intervention indicated

ADL = activities of daily living; CTCAE = Common Terminology Criteria for Adverse Events

DECREASED APPETITE OR WEIGHT LOSS MANAGEMENT

Questions you may want to consider when assessing baseline signs and symptoms:[13]

- Do you have any loss of appetite?
- What is your current weight? Is this typical for you?
- Have you gained or lost a significant amount of weight since your cancer diagnosis?
- What is your typical daily food intake?
- Do you feel hungry before meals?

Considerations for patient counselling[13]

- Offer information and advice about nutrition, diet, and managing weight loss
- Recommend nutritional supplements and additional vitamins
- Encourage patients and their caregivers to focus on enjoying food and the social interaction associated with eating and drinking

WEIGHT LOSS AND ANOREXIA GRADING

CTCAE v5.0 GRADES FOR WEIGHT LOSS[14]

Grade 1	• 5 to <10% from baseline; intervention not indicated
Grade 2	• 10 to <20% from baseline; nutritional support indicated
Grade 3	• ≥20% from baseline; tube feeding or total parenteral nutrition indicated

CTCAE v5.0 GRADES FOR ANOREXIA[14]

Grade 1	• Loss of appetite without alteration in eating habits
Grade 2	• Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated
Grade 3	• Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); tube feeding or total parenteral nutrition indicated
Grade 4	• Life-threatening consequences; urgent intervention indicated

CTCAE = Common Terminology Criteria for Adverse Events

Indications and clinical use:

CABOMETYX® (cabozantinib) is indicated for the treatment of advanced renal cell carcinoma (RCC) in adult patients who have received prior therapy.

CABOMETYX® is not indicated for pediatrics (<18 years of age).

Most serious warnings and precautions:

CABOMETYX® therapy: Initiated and supervised by physician experienced in anti-cancer medicines.

Patients with cardiac, severe renal and severe hepatic impairment: Not studied.

Thromboembolism, including deaths: Caution in patients at risk of venous and arterial thromboembolism. Permanently discontinue in case of acute myocardial infarction or thromboembolic complications.

Hypertension and hypertensive crisis: Monitor blood pressure prior to initiating and regularly during CABOMETYX® therapy. Do not initiate CABOMETYX® if hypertension is uncontrolled. Withhold CABOMETYX® for hypertension that is not adequately controlled with medical management; when controlled, resume with reduced dose. Permanently discontinue in severe unmanageable hypertension. Serious cases of artery dissection reported, with or without hypertension.

Gastrointestinal perforations and fistulas, including deaths: Evaluate patients with inflammatory bowel disease, tumour infiltration in GI tract, or GI surgery complications. Monitor for fistulas and perforations, including abscess and sepsis, and permanently discontinue therapy if these cannot be managed.

Hemorrhage, including deaths: Evaluate patients with a prior history of severe bleeding before initiating CABOMETYX®. Do not administer CABOMETYX® to patients with a recent history of hemorrhage, including hemoptysis, hematemesis, or melena. Permanently discontinue in the event of severe hemorrhage.

Hepatotoxicity: Monitor liver enzymes and bilirubin before and during treatment. Interrupt therapy and consider corticosteroids if liver enzymes increase. Consider dose reduction if resuming CABOMETYX®. Rare instances of vanishing bile duct syndrome have been reported. All cases have occurred in patients who have received immune checkpoint inhibitors, either before or concurrently with CABOMETYX® treatment.

Posterior Reversible Encephalopathy Syndrome: Consider in patients with multiple symptoms, including seizures, headache, visual disturbances, confusion, or altered mental function. Permanently discontinue in patients. Posterior reversible encephalopathy syndrome was reported in one patient in the pivotal differentiated thyroid cancer study.

Wound complications: Stop therapy at least 28 days before surgery. Discontinue in patients with wound healing complications requiring medical intervention.

Other relevant warnings and precautions:

- Evaluate patients closely during the first eight weeks of treatment to determine if dose modifications are warranted, as most events can occur early in the course of treatment.
- Caution in patients on drugs that prolong QTc or at increased risk of torsade de pointes. Monitor ECG and electrolytes regularly. Discontinue in patients who develop torsade de pointes, polymorphic ventricular tachycardia or serious arrhythmia.
- Caution in patients with heart disorders. Avoid drugs that decrease heart rate and/or prolong PR interval.
- Caution when driving or operating machinery.
- Withhold therapy depending on severity of adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated.
- Monitor oral health before and during treatment. Withhold therapy if osteonecrosis of the jaw develops.
- Monitor thyroid function before and during treatment.
- Withhold therapy for intolerable Grade 2 or Grade 3-4 diarrhea until resolution to Grade 1, then resume at reduced dose. Dose interruption, reduction, or discontinuation in cases of persistent or recurrent significant GI reactions.
- Monitor platelets during treatment and dose modify according to severity of thrombocytopenia.
- Monitor for signs and symptoms of hepatic encephalopathy.
- Hypocalcemia has been observed with CABOMETYX® at a higher frequency and/or increased severity (including Grade 3 and 4) in patients with thyroid cancer compared to patients with other cancers. Monitor blood calcium levels and consider treatment with appropriate replacement therapy and/or CABOMETYX® dose modification as clinically indicated, especially in thyroid cancer patients.
- Monitor urine protein. Permanently discontinue in patients with nephrotic syndrome.
- Withhold therapy in case of intolerable Grade 2 or Grade 3 palmar-plantar erythrodysesthesia syndrome. Upon resolution to Grade 1, resume at a reduced dose.
- Do not use in pregnant women. Avoid pregnancy in women of childbearing potential and in partners of male patients taking CABOMETYX®.
- Consider fertility preservation before treatment.
- Discontinue nursing during therapy, and for at least 4 months after therapy.

For more information:

Consult the Product Monograph at **health-products.canada.ca/dpd-bdpp/** for important information relating to adverse reactions, drug interactions and dosing information. The Product Monograph is also available by calling IPSEN Medical Information at 1-855-215-2288.

References: 1. CABOMETYX Product Monograph. Ipsen Biopharmaceuticals Canada Inc. 2. CABOMETYX Summary Basis of Decision, Ipsen Biopharmaceuticals Canada Inc., September 14, 2018. 3. Ljunberg B, *et al.* EAU Guidelines for the Treatment of Renal Cell Carcinoma. 2023 Update. Available at https://uroweb.org/guideline/renal-cell-carcinoma/#11. Accessed February 2, 2024. 4. Choueiri TK, *et al. Lancet Oncol* 2016;17:917-27. 5. Gibney GT, *et al. Ann Oncol* 2013;24:343-49. 6. Nakaigawa N, *et al. Cancer Res* 2006;66:3699-705. 7. Boysen G, *et al. Neoplasia* 2012;14:535-46. 8. Rankin EB, *et al. PNAS* 2014;111:13373-8. 9. Pennacchietti S, *et al. Cancer Cell* 2. 10. Zhou L, *et al. Oncogene* 2016;35:2687-97. 11. Escudier B, *et al. Ann Oncol* 2016;27:v58-68. 12. Choueiri TK, *et al. N Engl J Med* 2015;373:1814-1823 (Supplement). 13. BC Cancer Agency. Symptom Management. Available at http://www.bccancer.bc.ca/health-professionals/clinical-resources/nursing/symptom-management. Accessed February 2, 2024. 14. National Cancer Institute. Common Terminology Criteria of Adverse Events (CTCAE). Version 5.0. November 27, 2017. 15. Rabi DM, *et al. Can J Cardiol* 2020;36(5):596-624.

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