CABOMETYX®, in combination with nivolumab, is indicated for the first-line treatment of adult patients with advanced (not amenable to curative surgery or radiation therapy) or metastatic renal cell carcinoma (RCC).

CABOMETYX® + nivolumab:

For the treatment of advanced or metastatic RCC in the first-line setting

DEMONSTRATED EFFICACY

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

COMBINATION USE

CABOMETYX®, a VEGFR tyrosine kinase inhibitor, is now authorized for use in combination with an immuno-oncology agent.[1]*

HOME

EFFICACY RESULTS

KCRNC CONSENSUS STATEMENT

MECHANISM OF ACTION

SAFETY PROFILE

DOSING

IMPORTANT SAFETY INFORMATION

* Clinical significance unknown.
RCC = renal cell carcinoma; VEGF = vascular endothelial growth factor

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

CABOMETYX® + NIVOLUMAB IN COMBINATION:

Demonstrated efficacy in the first-line setting in advanced or metastatic RCC (CHECKMATE-9ER; open-label trial)

In patients with advanced (not amenable to curative surgery or radiation therapy) or metastatic RCC, CABOMETYX® + nivolumab demonstrated **statistically significant clinical benefits** across 3 endpoints after a minimum follow-up of 10.6 months.[1,2]*

Progression-free survival (PFS)

49% reduction in the risk of progression or death vs. sunitinib (Primary endpoint, per BICR)

HR=0.51 (95% CI: 0.41–0.64)‡; *p*<0.0001[§¶]
(Events: CABOMETYX® + nivolumab 144/323 vs. sunitinib 191/328)

Median PFS†

16.6 months CABOMETYX® + NIVOLUMAB	vs.	**8.3 months** sunitinib

Overall survival (OS)

40% reduction in the risk of death vs. sunitinib (Secondary endpoint)

HR=0.60 (98.89% CI: 0.40–0.89)‡; *p*<0.0010[§¶#]

Probability of OS at 12 months

85.7% CABOMETYX® + NIVOLUMAB	vs.	**75.6%** sunitinib

Median OS was not reached in either group.

Objective response rate (ORR)

(Secondary endpoint, per BICR; *p*<0.0001[Δ])

CABOMETYX® + NIVOLUMAB		sunitinib
55.7% (95% CI: 50.1–61.2)		27.1% (95% CI: 22.4–32.3)
8.0% Complete response		4.6% Complete response
47.7% Partial response		22.6% Partial response

CABOMETYX® + nivolumab n=323; sunitinib n=328

STUDY DESIGN | PATIENT DEMOGRAPHICS

* CHECKMATE-9ER: Phase 3 randomized, open-label study of CABOMETYX® combined with nivolumab versus sunitinib in adult patients with previously untreated advanced or metastatic RCC with clear cell component. Patients were randomized to CABOMETYX® 40 mg oral daily and nivolumab 240 mg intravenously every 2 weeks (n=323), or sunitinib 50 mg oral daily for the first 4 weeks of a 6-week cycle (4 weeks on treatment followed by 2 weeks off) (n=328). Tumour assessments were performed at baseline, after randomization at Week 12, then every 6 weeks until Week 60, and then every 12 weeks thereafter.

† Based on Kaplan-Meier estimates.

‡ Stratified Cox proportional hazards model. Hazard ratio is nivolumab and CABOMETYX® over sunitinib.

§ Log-rank test stratified by IMDC prognostic risk score (0, 1-2, 3-6), PD-L1 tumour expression (≥1% versus <1% or indeterminate) and region (US/Canada/W Europe/N Europe, ROW) as entered in the per protocol Interactive Response Technology (IRT) system.

¶ 2-sided *p*-values from stratified regular log-rank test.

Type-1 error controlled by hierarchical testing. OS interim analysis boundary for statistical significance *p*-value <0.0111.

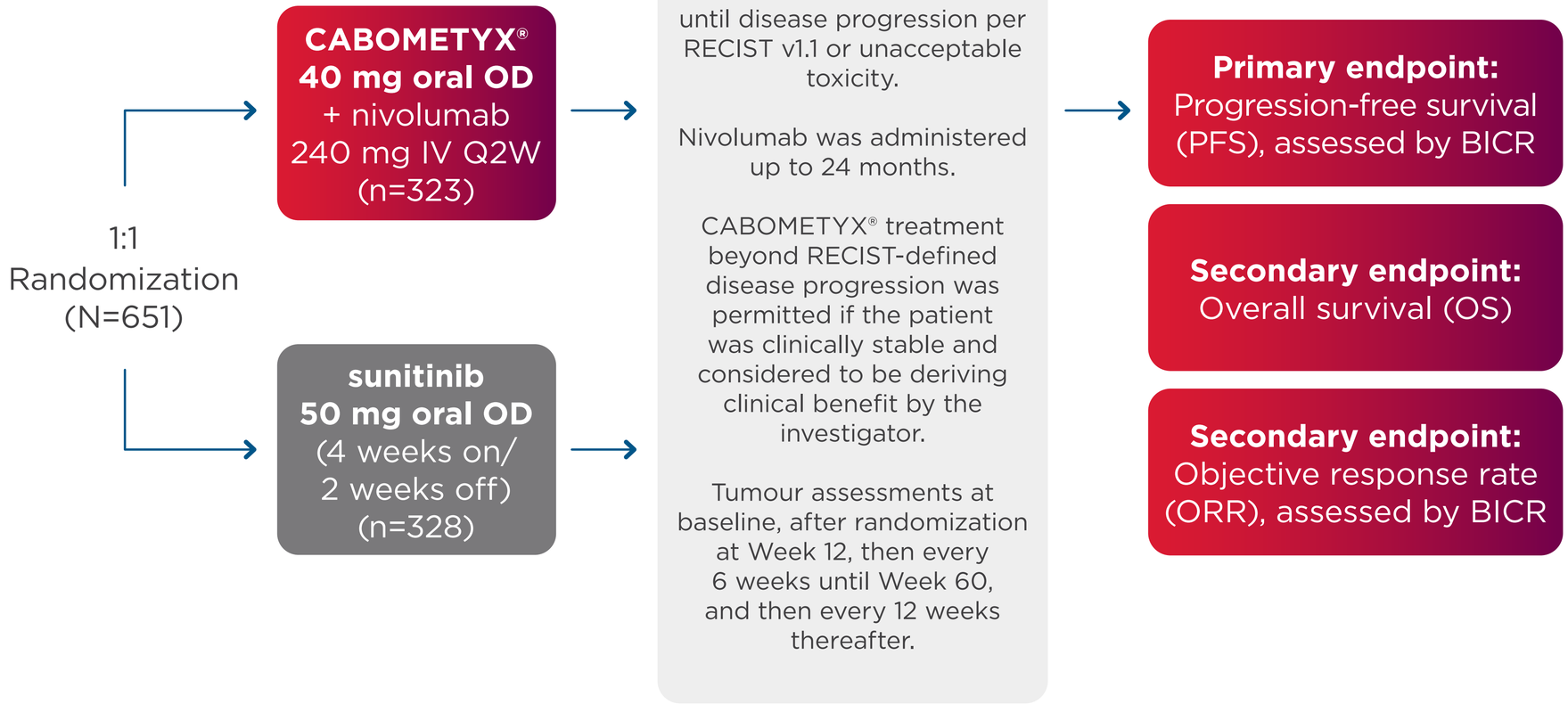
|| CI based on the Clopper and Pearson method.

Δ 2-sided *p*-value from Cochran-Mantel-Haenszel test.

BICR = blinded independent central review; CI = confidence interval; HR = hazard ratio; IMDC = International Metastatic Renal-Cell Carcinoma Database Consortium; IRT = Interactive Response Technology; PD-L1 = programmed death ligand 1; RCC = renal cell carcinoma

CHECKMATE-9ER STUDY: A PIVOTAL PHASE 3 TRIAL

A randomized, open-label trial that compared the efficacy and safety profile of CABOMETYX® + nivolumab vs. sunitinib in previously untreated advanced (not amenable to curative surgery or radiation therapy) or metastatic RCC.[1,2]



Adapted from the CABOMETYX® Product Monograph.
BICR = blinded independent central review; IV = intravenous; OD = once daily; Q2W = every two weeks; RCC = renal cell carcinoma; RECIST = Response Evaluation Criteria in Solid Tumors

CHECKMATE-9ER BASELINE CHARACTERISTICS: GENERALLY BALANCED BETWEEN THE TWO GROUPS

Select demographics and baseline characteristics (ITT population)[1,2]*

	CABOMETYX® + nivolumab (n=323)	Sunitinib (n=328)
Age		
Median	62 years	61 years
IMDC prognostic risk score		
Favourable: 0	22.9%	22.0%
Intermediate: 1 or 2	58.2%	57.3%
Poor: 3–6	18.9%	20.7%
Karnofsky performance-status score†		
90 or 100	79.6%	73.5%
70 or 80	20.4%	25.9%
Not reported	0.0%	0.6%
Most common sites of metastasis		
Lung	73.7%	75.9%
Lymph node	40.2%	39.9%
Bone	24.1%	22.0%
Liver	22.6%	16.2%
Adrenal gland	11.1%	11.0%

* The intention-to-treat population includes all the patients who underwent randomization. The IMDC prognostic risk score, PD-L1 status, and geographic region (stratification factors) were recorded at screening by means of interactive response technology.

† Karnofsky performance-status scores range from 0 to 100, with lower scores indicating greater disability.

‡ Data are for tumour sites defined at baseline by the investigators according to RECIST, version 1.1. The number of target or nontarget lesions at baseline was not reported for one patient in the nivolumab-plus-cabozantinib group and for three patients in the sunitinib group.

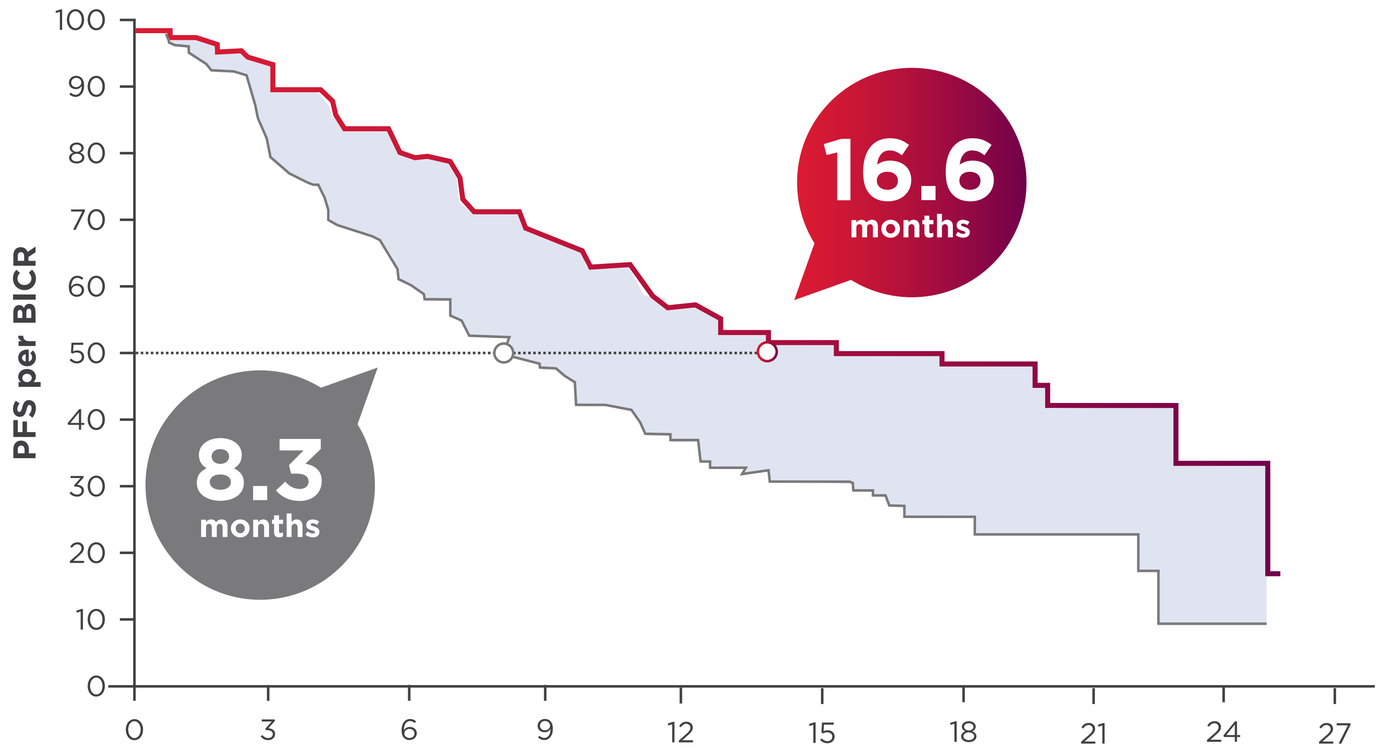
Adapted from the CABOMETYX® Product Monograph.

IMDC = International Metastatic Renal-Cell Carcinoma Database Consortium; ITT = intention to treat; PD-L1 = programmed death ligand 1; RECIST = Response Evaluation Criteria in Solid Tumors

CABOMETYX® + NIVOLUMAB EXTENDED TIME TO PFS VS. SUNITINIB

(HR=0.51 [95% CI: 0.41–0.64]*; *p*<0.0001†‡; primary endpoint)[1]

Median PFS (per BICR)§



Patients at risk

CABOMETYX® + nivolumab	323	279	234	196	144	77	35	11	4	0
sunitinib	328	228	159	122	79	31	10	4	1	0

CABOMETYX® + nivolumab (n=323)
sunitinib (n=328)

49% reduction in risk of progression or death

HR=0.51 (95% CI, 0.41–0.64)*; *p*<0.0001†‡

(Events: CABOMETYX® + nivolumab 144/323 vs. sunitinib 191/328)

Adapted from the CABOMETYX® Product Monograph

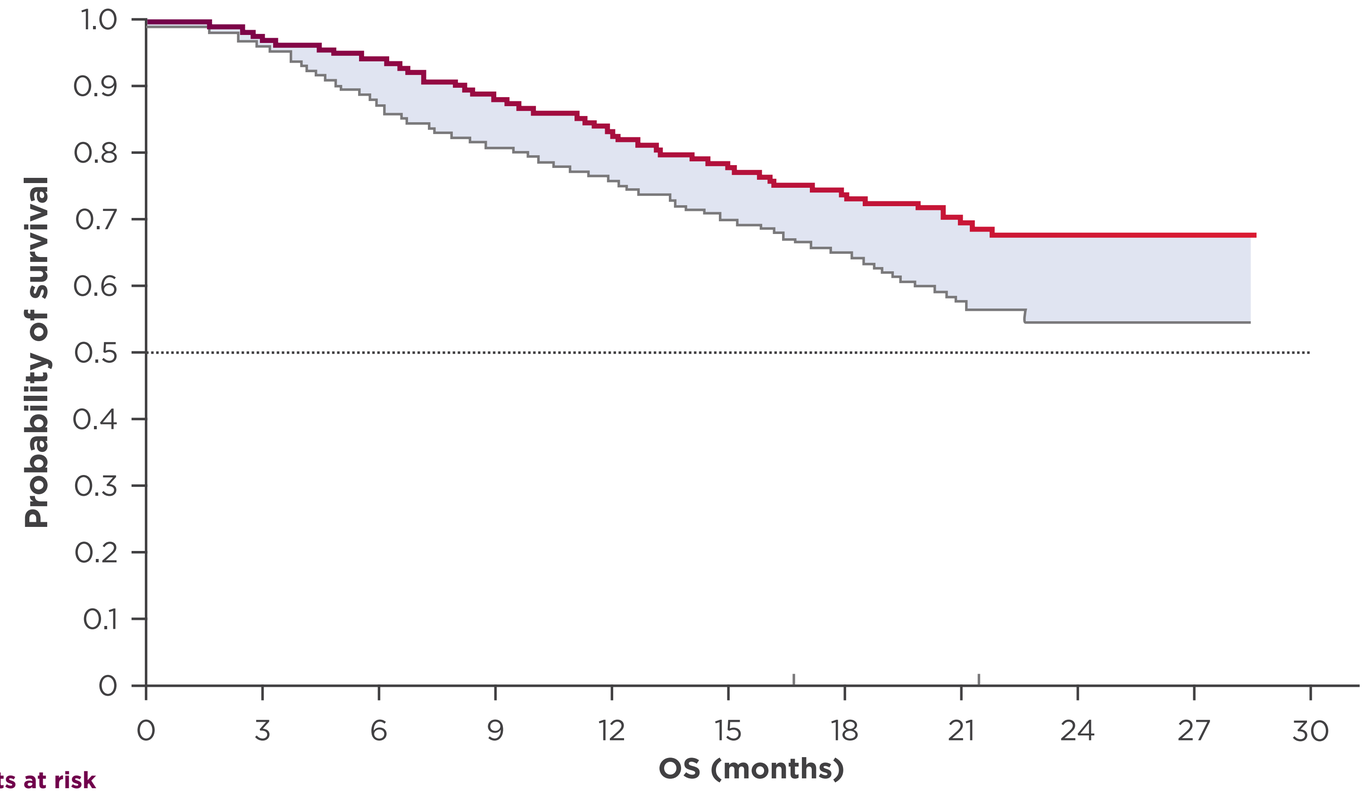
PFS SUBGROUP ANALYSIS

* Stratified Cox proportional hazards model. Hazard ratio is nivolumab and CABOMETYX® over sunitinib.
† Log-rank test stratified by IMDC prognostic risk score (0, 1-2, 3-6), PD-L1 tumour expression (≥1% versus <1% or indeterminate) and region (US/Canada/W Europe/N Europe, ROW) as entered in the per protocol Interactive Response Technology (IRT) system.
‡ 2-sided *p*-values from stratified regular log-rank test.
§ Based on Kaplan-Meier estimates.
BICR = blinded independent central review; CI = confidence interval; HR = hazard ratio; IMDC = International Metastatic Renal-Cell Carcinoma Database Consortium; IRT = Interactive Response Technology; PD-L1 = programmed death ligand 1; PFS, progression-free survival; ROW = rest of the world

CABOMETYX® + NIVOLUMAB EXTENDED OS VS. SUNITINIB[1]

(HR=0.60 [98.89% CI: 0.40–0.89]*; *p*<0.0010†‡§; secondary endpoint)[1]

Median OS not reached in either group



Patients at risk

CABOMETYX® + nivolumab	323	308	295	283	259	184	106	55	11	3	0
sunitinib	328	296	273	253	223	154	83	36	10	3	0

40% reduction in risk of death

HR=0.60 (98.89% CI, 0.40–0.89)*; *p*<0.0010†‡§

(Events: CABOMETYX® + nivolumab 67/323 vs. sunitinib 99/328)

Adapted from the CABOMETYX® Product Monograph.

OS SUBGROUP ANALYSIS

* Stratified Cox proportional hazards model. Hazard ratio is nivolumab and CABOMETYX® over sunitinib.

† Log-rank test stratified by IMDC prognostic risk score (0, 1-2, 3-6), PD-L1 tumour expression (≥1% versus <1% or indeterminate) and region (US/Canada/W Europe/N Europe, ROW) as entered in the per protocol Interactive Response Technology (IRT) system.

‡ 2-sided *p*-values from stratified regular.

§ Type-1 error controlled by hierarchical testing. OS interim analysis boundary for statistical significance *p*-value <0.0111.

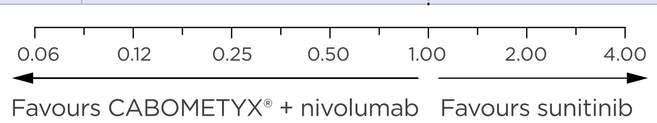
CI = confidence interval; HR = hazard ratio; IMDC = International Metastatic Renal-Cell Carcinoma Database Consortium; IRT = Interactive Response Technology; OS = overall survival; PD-L1 = programmed death ligand 1; ROW = rest of world

Pr CABOMETYX® (cabozantinib) tablets

PFS ACCORDING TO SUBGROUP

Additional exploratory PFS analyses across all three pre-specified IMDC risk subgroups[2]

Subgroup	No. of patients	CABOMETYX® + nivolumab	sunitinib	HR for disease progression or death (95% CI)
		No. of events/No. of patients		
Overall	651	144/323	191/328	0.51 (0.41–0.64)
IMDC prognostic risk				
Favourable	146	30/74	35/72	0.62 (0.38–1.01)
Intermediate	376	82/188	108/188	0.54 (0.40–0.72)
Poor	129	32/61	48/68	0.37 (0.23–0.58)



Adapted from Choueiri TK et al., 2021.[3]

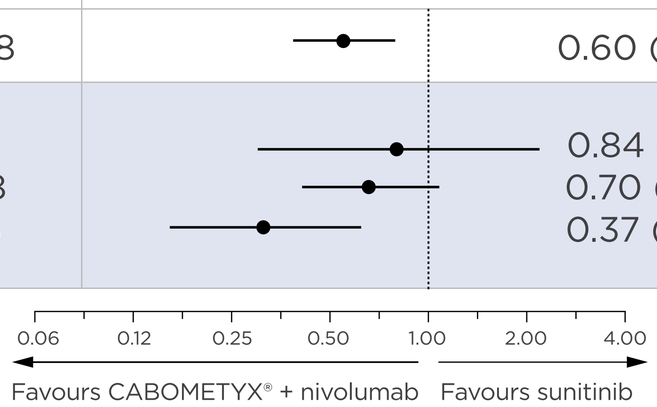
* Across all three pre-specified IMDC risk subgroups, additional exploratory analyses indicated a **consistent treatment benefit in PFS.**[1]

CI = confidence interval; HR = hazard ratio; IMDC = International Metastatic Renal-Cell Carcinoma Database Consortium; PFS = progression-free survival

OS ACCORDING TO SUBGROUP

Additional exploratory OS analyses across all three pre-specified IMDC risk subgroups[3]

Subgroup	No. of patients	CABOMETYX® + nivolumab	sunitinib	HR for death (95% CI)
		No. of events/No. of patients		
Overall	651	67/323	99/328	0.60 (0.44–0.82)
IMDC prognostic risk				
Favourable	146	10/74	11/72	0.84 (0.35–1.97)
Intermediate	376	40/188	51/188	0.70 (0.46–1.07)
Poor	129	17/61	37/68	0.37 (0.21–0.66)



Adapted from Choueiri TK et al., 2021.[2]

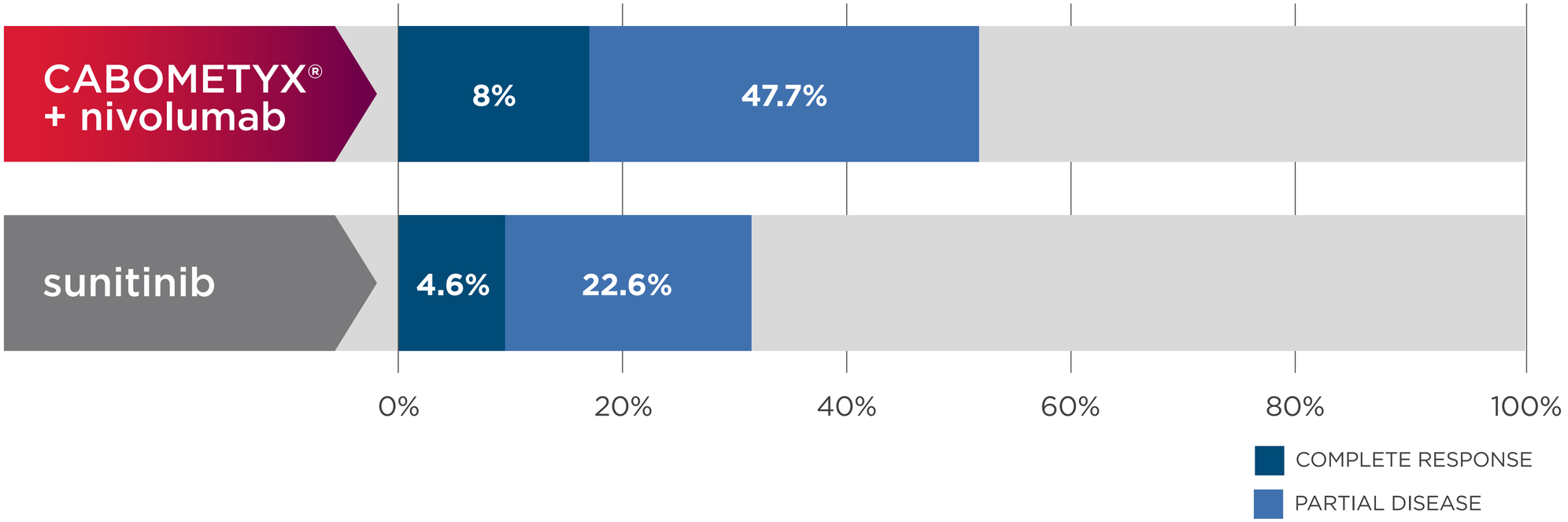
Additional exploratory analyses indicated a **consistent treatment benefit in OS** across all three pre-specified IMDC risk subgroups.[1]

CI = confidence interval; HR = hazard ratio; IMDC = International Metastatic Renal-Cell Carcinoma Database Consortium; OS = overall survival

CABOMETYX® + NIVOLUMAB: OTHER ORR FINDINGS VS. SUNITINIB

(BICR ASSESSED; SECONDARY ENDPOINT)[1]

55.7% (95% CI: 50.1%–61.2%) of CABOMETYX® + nivolumab patients demonstrated ORR (complete or partial response) vs. 27.1% (95% CI: 22.4%–32.3%) of sunitinib patients (p<0.0001).*



Adapted from the CABOMETYX® Product Monograph.

Median time to first response was 2.8 months with CABOMETYX® + nivolumab vs. 4.2 months with sunitinib.

* Response was assessed according to RECIST, version 1.1, by BICR of radiologic imaging. Percentages may not total 100 because of rounding.
BICR = blinded independent central review; CI = confidence interval; ORR = objective response rate; RECIST = Response Evaluation Criteria in Solid Tumors

CONSIDER CABOMETYX® + NIVOLUMAB IN THE FIRST-LINE SETTING IN ADVANCED OR METASTATIC RCC[1,3]

KCRNC Consensus Statement:
Cabozantinib + nivolumab is recommended as a preferred first-line option for advanced or metastatic clear cell RCC in patients at favourable risk and intermediate/poor risk (IMDC).[3]*

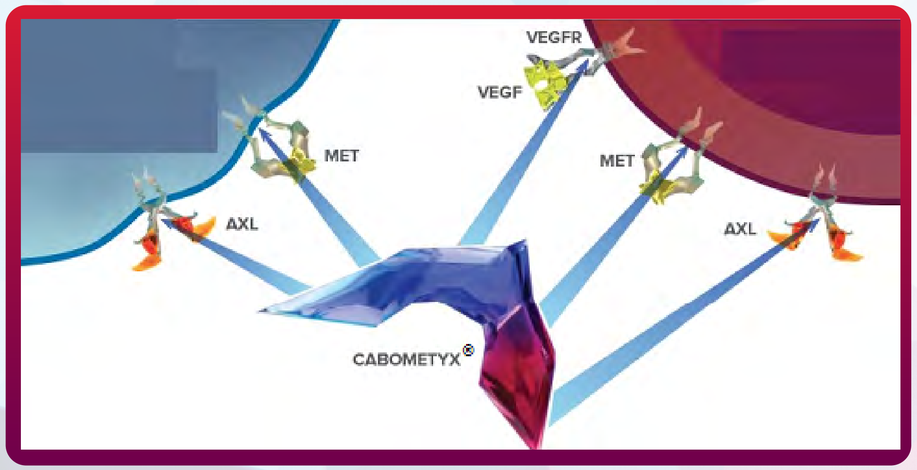
CABOMETYX®, in combination with nivolumab, is indicated for the first-line treatment of adult patients with advanced (not amenable to curative surgery or radiation therapy) or metastatic renal cell carcinoma (RCC).

* Comparative clinical significance unknown. See the KCRNC Consensus Statement for complete recommendations.
IMDC = International Metastatic Renal-Cell Carcinoma Database Consortium; KCRNC = Kidney Cancer Research Network of Canada

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

CABOMETYX® HAS A DISTINCT MOA WITH PRIMARY INHIBITION TARGETS OF VEGF, MET, AXL[1*]

- CABOMETYX® inhibits multiple receptor tyrosine kinases implicated in tumour growth and angiogenesis, pathologic bone remodelling, drug resistance, and metastatic progression of cancer.
- The VEGF, MET and AXL receptors primarily targeted by CABOMETYX® are involved in tumour progression and drug resistance in RCC.



Adapted from the CABOMETYX® Product Monograph.

In genetically engineered or syngeneic mouse models, CABOMETYX® demonstrated enhanced anti-tumour activity in combination with immuno-oncology therapies by decreasing tumour-infiltrating macrophages and myeloid-derived suppressor cells, where it promoted an immunopermissive tumour microenvironment.

* Clinical significance unknown.

AXL = GAS6 receptor; MET = hepatocyte growth factor receptor protein; RCC = renal cell carcinoma; VEGF = vascular endothelial growth factor; VEGFR = vascular endothelial growth factor receptor

CABOMETYX® + NIVOLUMAB IN CHECKMATE-9ER: AN ESTABLISHED SAFETY PROFILE

Most common adverse reactions in ≥10% of CABOMETYX® + nivolumab patients[1]

	CABOMETYX® + nivolumab (n=320)		sunitinib (n=320)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Diarrhea	64%	7%	47%	4%
Fatigue*	51%	8%	50%	8%
PPES	40%	8%	41%	8%
Stomatitis†	37%	3%	46%	4%
Hypertension‡	36%	13%	39%	14%
Rash§	36%	3%	14%	0%
Hypothyroidism¶	34%	0%	30%	0%
Musculoskeletal pain#	33%	4%	29%	3%
Decreased appetite	28%	2%	20%	1%
Nausea	27%	1%	31%	0%
Dysgeusia	24%	0%	22%	0%
Abdominal pain∆	22%	2%	15%	0%
Cough	20%	0%	17%	0%
Upper respiratory tract infection	20%	0%	8%	0%
Pruritus	19%	0%	4%	0%
Arthralgia	18%	0%	9%	0%

Adapted from the CABOMETYX® Product Monograph.

Adverse events of any cause of grade ≥3 occurred in 75.3% of the patients in the CABOMETYX® + nivolumab arm and in 70.6% of those in the sunitinib arm.[2]

DISCONTINUATION AND DOSE INTERRUPTION/REDUCTION

* Fatigue includes asthenia.
† Stomatitis is a composite term which includes mucosal inflammation, aphthous ulcer, mouth ulceration.
‡ Hypertension includes blood pressure increased, blood pressure systolic increased.
§ Rash is a composite term which includes dermatitis, dermatitis acneiform, dermatitis bullous, exfoliative rash, rash erythematous, rash follicular, rash macular, rash maculo-papular, rash papular, rash pruritic.
¶ Hypothyroidism includes primary hypothyroidism.
# Musculoskeletal pain is a composite term which includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, spinal pain.
∆ Abdominal pain includes abdominal discomfort, abdominal pain lower, abdominal pain upper.
|| Dyspepsia includes gastroesophageal reflux.
PPES = palmar-plantar erythrodysesthesia syndrome

CABOMETYX® + NIVOLUMAB IN CHECKMATE-9ER: AN ESTABLISHED SAFETY PROFILE

Most common adverse reactions in ≥10% of CABOMETYX® + nivolumab patients[1]

	CABOMETYX® + nivolumab (n=320)		sunitinib (n=320)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Dysphonia	17%	0%	3%	0%
Vomiting	17%	2%	21%	0%
Headache	16%	0%	12%	1%
Anemia	15%	2%	25%	4%
Dyspepsia‖	15%	0%	22%	0%
Dizziness	13%	1%	6%	0%
Constipation	12%	1%	13%	0%
Edema	12%	0%	10%	0%
Muscle spasms	12%	0%	2%	0%
Pyrexia	12%	1%	9%	1%
Dyspnea	11%	0%	9%	2%
Weight decreased	11%	1%	3%	0%
Hyperthyroidism	10%	1%	3%	0%
Proteinuria	10%	3%	8%	2%

Adapted from the CABOMETYX® Product Monograph.

Adverse events of any cause of grade ≥3 occurred in 75.3% of the patients in the CABOMETYX® + nivolumab arm and in 70.6% of those in the sunitinib arm.[2]

DISCONTINUATION AND DOSE INTERRUPTION/REDUCTION

* Fatigue includes asthenia.
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# Musculoskeletal pain is a composite term which includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, spinal pain.
Δ Abdominal pain includes abdominal discomfort, abdominal pain lower, abdominal pain upper.
‖ Dyspepsia includes gastroesophageal reflux.
PPES = palmar-plantar erythrodysesthesia syndrome

ADVERSE EVENTS MAY BE MANAGED WITH DOSE INTERRUPTIONS AND/OR REDUCTIONS, AS NEEDED*

CABOMETYX® + nivolumab safety population in the CHECKMATE-9ER study (n=320)[1,2]

	Permanent discontinuation	Dose interruption/reduction
CABOMETYX® or nivolumab	20%	83%
CABOMETYX® only	8%	46%
Nivolumab only	7%	3%
CABOMETYX® and nivolumab	6%	21% (same AE at the same time)† 6% (sequentially)

Adapted from the CABOMETYX® Product Monograph.

Dose reductions were required in 56% of patients taking CABOMETYX®.

- Dose reductions were not permitted with the nivolumab treatment.
- Median time to first dose reduction due to an AE was 98 days.

* To mitigate adverse reactions, CABOMETYX® and/or nivolumab was to be interrupted and upon resuming CABOMETYX® treatment the dose could be reduced to 20 mg daily or 20 mg every other day.
† Only diarrhea occurred at ≥5%.
AE = adverse event

PrCABOMETYX® (cabozantinib) tablets

CABOMETYX®: A ONCE-DAILY ORAL TREATMENT, IN COMBINATION WITH NIVOLUMAB, INDICATED FOR ADVANCED OR METASTATIC RCC

The recommended starting dose for CABOMETYX® in combination with nivolumab is **40 mg once daily without food** (administered at least 1 hour before or at least 2 hours after eating).[1]

Nivolumab

240 mg
Every 2 weeks
(30-min IV infusion)

or

480 mg
Every 4 weeks
(30-min IV infusion)

+

CABOMETYX®

40 mg daily
Once daily

Taken first, during the day

Taken on an empty stomach, in the evening

- Continue CABOMETYX® treatment until disease progression or unacceptable toxicity.
- Continue nivolumab treatment until disease progression or unacceptable toxicity for up to 2 years.
- Evaluate patients closely during the first 8 weeks to determine if dose modifications are necessary.[1]

DOSAGE MODIFICATIONS FOR ADVERSE REACTIONS

Refer to the nivolumab Product Monograph for recommended nivolumab dosing and product information prior to initiation. Refer to the CABOMETYX® Product Monograph for complete dosing and administration information.

IV = intravenous; RCC = renal cell carcinoma

PrCABOMETYX® (cabozantinib) tablets

DOSAGE MODIFICATIONS FOR ADVERSE REACTIONS

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

- Dose interruptions are recommended for management of CTCAE grade ≥3 toxicities or intolerable grade 2 toxicities.
- Dose reductions are recommended for events that could become serious or intolerable, if persistent.

Dose reductions following resolution/improvement (i.e., a return to baseline or resolution to Grade 1) of an adverse drug reaction

Recommended starting dose

CABOMETYX®
40 mg
daily in combination with nivolumab

First dosage reduction

20 mg daily

Second dosage reduction

20 mg daily
every other day*

Refer to the nivolumab Product Monograph for recommended nivolumab dosing and product information prior to initiation. Refer to the CABOMETYX® Product Monograph for complete dosing information which includes modifications for coadministration with strong CYP3A4 inhibitors and inducers and hepatic adverse reactions.

* If previously receiving lowest dose, resume at same dose. If lowest dose not tolerated, discontinue CABOMETYX®.
CTCAE = Common Terminology Criteria for Adverse Events

PrCABOMETYX® (cabozantinib) tablets

Clinical use:

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. Consider more frequent monitoring with CABOMETYX® and nivolumab combination therapy. 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 occurred in patients who 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.

Refer to the nivolumab Product Monograph for nivolumab product information.

ECG = electrocardiogram; GI = gastrointestinal

References: 1. CABOMETYX® Product Monograph. Ipsen Biopharmaceuticals Canada Inc. **2.** Choueiri TK, et al. *N Engl J Med.* 2021;384:829-841. **3.** Canil C, et al. *Can Urol Assoc J.* 2021;15(4):84-97.

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