Cabozantinib (Cabometyx®) as monotherapy for the treatment of locally advanced or metastatic differentiated thyroid carcinoma (DTC)

General information

Drug description [1]	Indication [2]
Cabozantinib (Cabometyx®) is a small molecule that inhibits multiple receptor tyrosine kinases implicated in tumour growth and angiogenesis, pathologic bone remodelling, drug resistance, and metastatic progression of cancer.	Cabozantinib (Cabometyx®) is indicated as monotherapy for the treatment of adult patients with locally advanced or metastatic DTC, refractory or not eligible to radioactive iodine (RAI) who have progressed during or after prior systemic therapy.

Current treatment [3]

- NICE recommends Lenvatinib and sorafenib as treatment options for progressive, locally advanced, or metastatic DTC in adults whose disease does not respond to RAI only if they have not had tyrosine kinase inhibitor before or have had to stop taking a tyrosine kinase inhibitor within 3 months of starting it because of toxicity.
- Selpercatinib is recommended for advanced RET fusion-positive thyroid cancer in adults who need systemic therapy after sorafenib or lenvatinib, and for advanced RET-mutant medullary thyroid cancer in people ≥12 years who need systemic therapy after cabozantinib or vandetanib.

Regulatory status

EMA [2]

Approval status for this indication: On 24 March 2022, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Cabometyx®.

<u>The CHMP adopted a new indication:</u>

- Cabometyx® is indicated as monotherapy for the treatment of adult patients with locally advanced or metastatic DTC, refractory or not eligible to RAI who have progressed during or after prior systemic therapy.

Other indications: Cabometyx® is indicated:

- Renal cell carcinoma (RCC)
  - as monotherapy for advanced RCC
    - as first-line treatment of adult patients with intermediate or poor risk
    - in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy.
  - in combination with nivolumab, for the first-line treatment of advanced RCC in adults.
- Hepatocellular carcinoma (HCC)
  - as monotherapy for the treatment of HCC in adults who have previously been treated with sorafenib.

✓ **Accelerated assessment**[1]

FDA [4, 5]

Approval status for this indication: On 17 September 2021, the FDA approved cabozantinib (Cabometyx®) for adult and paediatric patients 12 years of age and older with locally advanced or metastatic DTC that has progressed following prior VEGFR-targeted therapy and who are ineligible or refractory to RAI.

Other indications: Cabometyx® is indicated for the treatment of

- patients with advanced RCC
- patients with advanced RCC, as a first-line treatment in combination with nivolumab
- patients with HCC who have been previously treated with sorafenib

Costs [6]

[1] This medicine had an accelerated assessment, meaning that it is a medicine of major interest for public health, so its timeframe for review was 150 evaluation days rather than 210.

30 Cabometyx® tablets 60 mg = **€ 5,978.76** (ex-factory price)

Warnings and precautions [4]

- **Haemorrhage**
  - Do not administer Cabometyx® if recent history of haemorrhage.
- **Perforations and fistulas**
  - Monitor for symptoms. Discontinue Cabometyx® for Grade 4 fistula or perforation.
- **Thrombotic events**
  - Discontinue Cabometyx® for myocardial infarction or serious venous or arterial thromboembolic events.
- **Hypertension and hypertensive crisis**
  - Monitor blood pressure regularly. Interrupt for hypertension that is not adequately controlled with anti-hypertensive therapy.
  - Discontinue Cabometyx® for hypertensive crisis or severe hypertension that cannot be controlled with anti-hypertensive therapy.
- **Diarrhoea**
  - May be severe. Interrupt Cabometyx® until diarrhoea resolves or decreases to ≤Grade 1, resume at reduced dose. Recommend standard antidiarrheal treatments.
- **Palmar-plantar erythrodysesthesia (PPE)**
  - Interrupt Cabometyx® treatment until PPE resolves or decreases to Grade 1.
- **Hepatotoxicity**
  - When used in combination with nivolumab, higher frequencies of Grade 3 and 4 ALT and AST elevation may occur than with Cabometyx® alone.
  - Monitor liver enzymes before initiation of and periodically throughout treatment. Consider withholding Cabometyx® and/or nivolumab, initiating corticosteroid therapy, and/or permanently discontinuing the combination for severe or life-threatening hepatotoxicity.
- **Adrenal insufficiency**
  - When used in combination with nivolumab, primary or secondary adrenal insufficiency may occur. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold Cabometyx® and/or nivolumab depending on severity.
- **Proteinuria**
  - Monitor urine protein. Interrupt Cabometyx® until proteinuria resolves to ≤ Grade 1, resume Cabometyx® at a reduced dose.
  - Discontinue for nephrotic syndrome.
- **Osteonecrosis of the jaw (ONJ)**
  - Withhold Cabometyx® for at least 3 weeks prior to invasive dental procedures and for development of ONJ.
- **Impaired wound healing**
  - Withhold Cabometyx® for at least 3 weeks before elective surgery. Do not administer for at least 2 weeks following major surgery and adequate wound healing. The safety of resumption of Cabometyx® after resolution of wound healing complications has not been established.
- **Reversible posterior leukoencephalopathy syndrome**
  - Discontinue Cabometyx®.
- **Thyroid dysfunction**
  - Monitor thyroid function before and during treatment with Cabometyx®.
- **Hypocalcemia**
  - Withhold Cabometyx® and resume at reduced dose upon recovery or permanently discontinue Cabometyx® depending on severity.
- **Embryo-foetal toxicity**
  - Can cause foetal harm. Advise females of reproductive potential of the potential risk to a foetus and to use effective contraception.

Study characteristics [7-9]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)

COSMIC-311 NCT03690388	187 (2:1)	oral cabozantinib at a dose of 60 mg once daily	placebo	objective response rate[2] in the first 100 randomly assigned patients (objective response rate intention-to-treat, OITT population) + PFS[3] in all patients (intention-to-treat, ITT population), both assessed by BIRC	**ongoing**[4], global, multicentre, randomised, double-blind, placebo-controlled, phase 3 trial	-	Exelixis	[8]

Efficacy (I vs. C)	**Safety** (I vs. C) (ITT-population)
<u>OITT population (n=67 vs. n=33), median follow-up 8.9 months</u> Partial response: 15% vs. 0% Objective response rate: 15% (99% CI, 5.8–29.3) vs. 0% (99% CI, 0–14.8); p=0.028 (**not** significant) Median duration of response: NR (95% CI 4.1–NE) vs. NA Reduction in target lesions in patients with at least one post-baseline target lesion: 76% vs. 29% Disease stabilisation rate: 60% (95% CI, 47.0–71.5) vs. 27% (95% CI, 13.3–45.5) Median time to response: 2.5 months (IQR, 1.8–3.6) vs. NA **<u>ITT population (n=125 vs. n=62), median follow-up 6.2 months</u>** Interim analysis of PFS by BIRC in the ITT population showed a **significant** improvement with cabozantinib versus placebo: Median PFS: not reached (96% CI, 5.7–NE) vs. 1.9 months (1.8–3.6), HR 0.22, 96% CI, 0.13–0.36, p<0.0001 PFS estimates at 6 months: 57% (96% CI. 43–69) vs. 17% (7–30) Partial response: 9% vs. 0% Median duration of response: NR (95% CI 4.1–NE) vs. NA Median time to response: 1.9 months (IQR, 1.8-3.6) vs. NA Disease stabilisation rate: 43% (95% CI, 34.4–52.4) vs. 16% (95% CI 8.0–27.7) Decrease in serum thyroglobulin concentrations: 62% vs. 19%	**AEs of any grade**: n=117/125 (94%) vs. 58/62 (93%), **AEs of grade 3 or 4:** n=71/125 (57%) vs. n=16/62 (26%) **Serious treatment-related AEs**: n=20/125 (16%) vs. n=1/62 (2%) **Discontinuation due to treatment-emergent AEs unrelated to DTC:** n=6/125 (5%) vs. 0 **Deaths (none of these grade 5 events were considered treatment related)[5]:** n=9/125 (7%) vs. n=7/62 (11%)

[2] Confirmed response per RECIST version 1.1.

[3] Defined as time to earlier of disease progression per RECIST version 1.1 or death.

[4] The COSMIC-311 trial is ongoing; estimated study completion date is 12/2022.

[5] In the cabozantinib group, 5 patients died from disease progression or thyroid cancer. The other 4 patients had the following grade 5 adverse events leading to death: arterial haemorrhage, cardiorespiratory arrest, pneumonia, and pulmonary embolism (1 patient for each). In the placebo group, 4 patients died from disease progression or thyroid cancer. The other 3 patients had the following grade 5 events leading to death: cardiac arrest, cerebrovascular accident, and general physical health deterioration (1 patient for each).

OS Deaths at data cut-off: 14% vs. 23% Median OS: NR (95% CI NE–NE) vs. NR, HR 0.54; 95% CI, 0.27–1.11) OS estimates at 6 months: 85% (95% CI 75.0–91.0) vs. 73% (58.4–83.7) Patients who used subsequent systemic anticancer therapy: 2% vs. 6%; this does not include the 19 patients (31%) in the placebo group who crossed over to open-label cabozantinib. **QoL**: analyses in progress **Updated analysis (full ITT, n=170 vs. n=88) [10]:** Median PFS: 11.0 months (96% CI, 7.4-13.8) vs. 1.9 months (1.9-3.7); HR 0.22 (96% CI, 0.15-0.32) OS events: 22% vs. 24%; HR 0.76 (95% CI, 0.45-1.31)	

ESMO-MCBS version 1.1 [11]											
Scale	Int.	Form	MG ST	MG	HR (96% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Not applicable because median PFS was not reached in the intervention group.											

Risk of bias (RCT) [12]					
Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes	yes	yes	unclear[6]	yes[7]	unclear
					First published: 04/2022 **Last updated**: 06/2022

Abbreviations: AE=adverse event, AJ=adjustment, ALT=alanine aminotransferase, AST=aspartate aminotransferase, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, DTC=differentiated thyroid carcinoma, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, HCC=hepatocellular carcinoma, HR=hazard ratio, I=intervention, Int.=intention, ITT=intention-to-treat, MG=median gain, n=number of patients, NA=not applicable, NE=not estimable, NICE=National Institute of Health and Care Excellence, NR=not reached, OITT=objective response rate intention-to-treat, ONJ=osteonecrosis of the jaw, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, PPE=palmar-plantar erythrodysesthesia, QoL=quality of life, RAI=radioactive iodine, RCC=renal cell cancer, RECIST=Response Evaluation Criteria in Solid Tumours, RET=rearranged during transfection, SAE=serious adverse event, ST=standard treatment, VEGF=vascular endothelial growth factor

References:

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[6] The COSMIC-311 trial is ongoing until 12/2022; currently only interim/primary analysis data is available. Results not yet available for all prespecified endpoints.

[7] The funder of the study provided cabozantinib and placebo and had a role in study design, data collection, and data analysis. Some of the authors and the steering committee in collaboration with the funder designed the trial. The authors and the funder were responsible for data collection, data analysis, and data interpretation. The funder also provided financial support for medical writing.

7. Supplement to: Brose MS, Robinson B, Sherman SI, et al. Cabozantinib for radioiodinerefractory differentiated thyroid cancer (COSMIC-311): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2021; published online July 5.
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