

Health Technology Briefing May 2023

Cabozantinib with nivolumab and ipilimumab for previously untreated advanced or metastatic renal cell carcinoma

Company/Developer Ipsen Ltd

New Active Substance Significant Licence Extension (SLE)

NIHRIO ID: 27428

NICE ID: N/A

UKPS ID: 665473

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Cabozantinib in combination with nivolumab and ipilimumab is in clinical development for the treatment of adults with previously untreated advanced or metastatic renal cell carcinoma (RCC) with intermediate or poor risk. Advanced cancer is when the cancer is late stage and can't be surgically removed, whereas metastatic is when the cancer has also spread to other areas of the body. RCC is also known as kidney cancer and is one of the 7th most common cancers in the UK. RCC usually affects adults in their 60s and 70s, and people aged 85 to 89 have the highest rate of kidney cancer. In early stages it can be asymptomatic (no symptoms), but symptoms include blood in urine, lower back or side pain, high blood pressure, loss of appetite and weight, bone pain, breathing difficulties, tiredness, high temperature, night sweats, swollen neck glands and coughing up blood. There is a need for additional treatment options to improve patient outcomes.

Cabozantinib is a tyrosine kinase inhibitor, meaning it blocks the activity of enzymes called tyrosine kinases. These enzymes can be found in certain receptors in cancer cells, where they are involved in activating processes such as cell division and growth of blood vessels supplying the cancer. By blocking this activity cabozantinib reduces the growth and spread of cancer. It will be used in combination with nivolumab and ipilimumab. Oral cabozantinib will be given at a dose of 40mg once a day and nivolumab and ipilimumab will be given intravenously (into the vein) every three weeks. If licenced cabozantinib in combination with nivolumab and ipilimumab would offer an additional treatment option for adults with intermediate or poor risk previously untreated advanced or metastatic RCC.

Proposed Indication

Previously untreated advanced or metastatic renal cell carcinoma (RCC) of intermediate or poor risk (according to the International Metastatic RCC Database Consortium categories).¹

Technology

Description

Cabozantinib (Cabometyx, Cometriq) is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs) implicated in tumour growth and angiogenesis, pathologic bone remodelling, drug resistance, and metastatic progression of cancer. Cabozantinib was evaluated for its inhibitory activity against a variety of kinases and was identified as an inhibitor of MET (hepatocyte growth factor receptor protein) and VEGF (vascular endothelial growth factor) receptors. In addition, cabozantinib inhibits other tyrosine kinases including the GAS6 receptor (AXL), RET, ROS1, TYRO3, MER, the stem cell factor receptor (KIT), TRKB, Fms-like tyrosine kinase-3 (FLT3), and TIE-2.²

Cabozantinib in combination with nivolumab and ipilimumab is in clinical development for the first-line treatment of RCC in patients with intermediate or poor risk. In the phase III clinical trial (COSMIC-313, NCT03937219,) patients received 40mg cabozantinib oral tablet once daily, nivolumab intravenous (IV) infusion (3mg/kg) and ipilimumab IV infusion (1mg/kg) once every 3 weeks (Q3W) for four cycles, followed by 480mg nivolumab IV infusion on week 4 for up to 2 years.^{1,3}

Key Innovation

Cabozantinib improved outcomes compared to sunitinib in previously untreated patients with advanced RCC as a single agent in a phase II clinical trial (CABOSUN, NCT01835158) and in combination with nivolumab in a phase III clinical trial (CheckMate 9ER, NCT03141177).^{4,5} There is a need for additional effective first line treatment options for patients with intermediate or poor risk RCC to improve positive outcomes.^{6,7} If licensed, cabozantinib in combination with nivolumab and ipilimumab will offer a new treatment option for patients with intermediate or poor risk untreated advanced or metastatic RCC.

Regulatory & Development Status

Cabozantinib has the following Marketing Authorisation in the EU/UK for adults:^{2,8}

- As a monotherapy for advanced RCC:
 - As first line treatment for patients with intermediate or poor risk.
 - Following prior VEGF-targeted therapy.
- In combination with nivolumab for the first line treatment of advanced RCC.
- As a monotherapy for the treatment of hepatocellular carcinoma (HCC) for patients who have previously been treated with sorafenib.
- As a monotherapy for the treatment of locally advanced or metastatic differentiated thyroid carcinoma (DTC), refractory or not eligible to radioactive iodine who have progressed during or after prior systemic therapy.
- For the treatment of progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma

Cabozantinib in combination with nivolumab and ipilimumab is in phase II/III clinical development for:⁹

- Gynecologic carcinosarcoma
- Neuroendocrine carcinoma
- DTC
- Bladder adenocarcinoma

- HCC
- Sarcoma
- Melanoma

Patient Group

Disease Area and Clinical Need

RCC (also known as kidney cancer) is the 7th most common cancer in the UK.¹⁰ It is caused by DNA mutations of cells in the kidney, which leads to cell growth and tumours. These cells can continue to grow (advance) and may spread to other areas of the body (metastasis).¹¹ Early stages of RCC are often asymptomatic, however symptoms can include blood in urine (haematuria), pain in lower back or side, high blood pressure (hypertension), loss of appetite and weight, bone pain, breathing difficulties, tiredness, high temperature, night sweats, swollen neck glands, and coughing up blood.^{11,12} RCC usually affects adults in their 60s or 70s, and is rare in people under 50.¹³ Risk factors include smoking, obesity, hypertension, family history of RCC, some inherited genetic conditions (such as hereditary papillary RCC and Von Hippel-Lindau disease), exposure to certain chemicals e.g. asbestos or cadmium, long-term dialysis, and polycystic kidney disease.^{11,13}

In England, 2021-22, there were 26,315 finished consultant episodes (FCE) for kidney cancer (ICD-10 code C64) resulting in 14,550 day cases and 47,072 FCE bed days.¹⁴ In England, 2021, there were 3,340 deaths with kidney cancer as the leading cause.¹⁵ In England (2013-17), around 75% of patients with stage III RCC (advanced) will survive for 5 years or more, but this falls to approximately 10% of people with stage IV (metastatic) RCC.¹⁶ In the UK (2016-18) incidence rates for kidney cancer were highest in people aged 85 to 89.¹⁰

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) currently recommends the following pharmacological treatments for untreated advanced or metastatic RCC:¹⁷

- Pazopanib
- Cabozantinib
- Tivozanib
- Avelumab with axitinib

NICE currently recommends the following treatments for intermediate or poor risk, untreated advanced or metastatic RCC:¹⁷

- Sunitinib
- Nivolumab with ipilimumab
- Lenvatinib with pembrolizumab

Clinical Trial Information

Trial

COSMIC-313; [NCT03937219](#); A Randomized, Double-Blind, Controlled Phase 3 Study of Cabozantinib in Combination With Nivolumab and Ipilimumab Versus Nivolumab and Ipilimumab in Subjects With Previously Untreated Advanced or Metastatic Renal Cell Carcinoma of Intermediate or Poor Risk

Phase III – Active, not recruiting

Location(s): 11 EU countries, UK, USA, Canada, and other countries

	Primary completion date: January 2022
Trial Design	Randomised, triple-masked (participant, investigator, outcomes assessor). Parallel assignment, active comparator controlled.
Population	N=855 (actual) ¹⁸ ; aged 18 years and older; confirmed advanced or metastatic RCC (intermediate- or poor-risk (according to the International Metastatic RCC Database Consortium categories).
Intervention(s)	40mg cabozantinib oral tablet once daily, nivolumab intravenous (IV) infusion (3mg/kg) on week 3 (Q3W) and ipilimumab IV infusion (1mg/kg) for four cycles, followed by 480mg nivolumab IV infusion on week 4. ³
Comparator(s)	Cabozantinib-matched placebo.
Outcome(s)	<p>Primary Outcome Measure:</p> <ul style="list-style-type: none"> Duration of Progression-Free Survival (PFS) per RECIST 1.1 as determined by blinded independent radiology committee (BIRC) [Time Frame: Up to 23 months after first subject randomised] <p>See trial record for full list of outcomes.</p>
Results (efficacy)	The probability of PFS at 12 months was 0.57 in the experimental group and 0.49 in the control group (hazard ratio for disease progression or death, 0.73; 95% confidence interval, 0.57 to 0.94; P=0.01); 43% of the patients in the experimental group and 36% in the control group had a response. ¹⁸
Results (safety)	Grade 3 or 4 adverse events occurred in 79% of the patients in the experimental group and in 56% in the control group. A grade 5 event of any cause occurred in 27 patients (6%) in the experimental group and in 34 (8%) in the control group. Adverse events related to the trial regimen that led to discontinuation of any component occurred in 45% of the patients in the experimental group and in 24% in the control group. ¹⁸

Estimated Cost

The NHS indicative cost of a packet of 30 20mg cabozantinib tablets is £5,143.00.¹⁹ The NHS indicative cost of a vial of nivolumab (100mg/10ml) is £1,097.00, and a vial of ipilimumab (200mg/40ml) is £15,000.^{20,21}

Relevant Guidance

NICE Guidance

- NICE technology appraisal guidance in development. Cabozantinib with nivolumab for untreated advanced renal cell carcinoma (GID-TA11158). Expected date of issue to be confirmed.
- NICE technology appraisal guidance. Lenvatinib with pembrolizumab for untreated advanced renal cell carcinoma (TA858). January 2023.
- NICE technology appraisal guidance. Nivolumab with ipilimumab for untreated advanced renal cell carcinoma (TA780). March 2022.

- NICE technology appraisal guidance. Avelumab with axitinib for untreated advanced renal cell carcinoma (TA645). September 2020.
- NICE technology appraisal guidance. Tivozanib for treating advanced renal cell carcinoma (TA512). March 2018.
- NICE technology appraisal guidance. Cabozantinib for previously treated advanced renal cell carcinoma (TA463). August 2017.
- NICE technology appraisal guidance. Pazopanib for the first-line treatment of advanced renal cell carcinoma (TA215). August 2013.
- NICE technology appraisal guidance. Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma (TA169). March 2009.
- NICE interventional procedures guidance. Irreversible electroporation for treating renal cancer (IPG443). February 2013.
- NICE interventional procedures guidance. Laparoscopic cryotherapy for renal cancer (IPG405). August 2011.
- NICE interventional procedures guidance. Percutaneous cryotherapy for renal cancer (IPG402). July 2011.
- NICE interventional procedures guidance. Laparoscopic partial nephrectomy (IPG151). January 2006.
- NICE interventional procedures guidance. Laparoscopic nephrectomy (including nephroureterectomy) (IPG136). August 2005.
- NICE pathways pilot. Renal cell carcinoma (GID-TA11186). Expected date of publication to be confirmed.

NHS England (Policy/Commissioning) Guidance

- NHS England. Specialised kidney, bladder, and prostate cancer services (adults); Service specification. 170114S. February 2019.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Specialised kidney, bladder, and prostate cancer services (adult). B14/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All ages). Service specification. B01/S/a.

Other Guidance

- European Association of Urology (EAU). EUA Guidelines on Renal Cell Carcinoma. March 2023.²²
- European Society for Medical Oncology (ESMO). eUpdate – Renal Cell Carcinoma Treatment Recommendations. September 2021.²³
- ESMO. Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. May 2019.²⁴

Additional Information

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