Health Technology Briefing
October 2024

Savolitinib with durvalumab for treating unresectable locally advanced or metastatic MET-driven papillary renal cell carcinoma

Company/Developer	AstraZeneca UK Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 33820	NICE ID: N/A	UKPS ID: 670215

Licensing and Market Availability Plans

Currently in phase III clinical development

Summary

Savolitinib in combination with durvalumab is currently in clinical development for the treatment of patients with unresectable and locally advanced or metastatic mesenchymal-epithelial transition (MET)-driven papillary renal cell carcinoma (PRCC). Renal cell carcinoma is a common type of kidney cancer. Unresectable means the cancer cannot be removed with surgery. Locally advanced means the cancer has spread into the surrounding area. Metastatic cancer means cells have broken away from the original (primary) tumour and travelled around the body to form tumours in new regions. In most cases of locally advanced PRCC, surgery is not possible and therapeutic options are often limited meaning there is an unmet clinical need.

Savolitinib is an oral MET-Tyrosine kinase inhibitor medication that can block the MET-pathway responsible for the growth of the tumours in MET-driven PRCC. Durvalumab is a type of protein (monoclonal antibody) administered by intravenous infusion to increase the ability of the immune system to kill cancer cells. The combination of savolitinib and durvalumab may be effective in overcoming drug resistance. If licensed, savolitinib in combination with durvalumab will offer an additional treatment option for patients with unresectable and locally advanced or metastatic MET-driven PRCC.

Proposed Indication

Treatment for patients with MET-driven, unresectable and locally advanced or metastatic papillary renal cell carcinoma.[1]

Technology

Description

Savolitinib (Orpathys) is an oral medication classified as a selective mesenchymal epithelial transition (MET) factor inhibitor.[2-4] MET tyrosine kinase inhibitors (TKI)s are classified into three types based on their mechanism of action. Type I MET TKIs act as adenosine triphosphate (ATP) competitors and target the ATP binding pocket of the active form of the MET-TK receptor. Savolitinib belongs to the Type Ib MET TKI class and, specifically interacts with the amino acid residue Y1230 which effectively inhibits the activity of the MET receptor. By targeting this specific region, savolitinib successfully hinders the signalling pathway associated with MET activation.[4,5] Durvalumab (Imfinzi) is a fully human, immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that selectively blocks the interaction of PD-L1 with PD-1 and CD80 (B7.1). Durvalumab does not induce antibody dependent cell-mediated cytotoxicity (ADCC). Selective blockade of PD-L1/PD-1 and PD-L1/CD80 interactions enhances antitumour immune responses and increases T-cell activation.[6]

Savolitinib in combination with durvalumab is currently in clinical development for the treatment of patients with unresectable and locally advanced or metastatic MET-driven PRCC. In the phase III clinical trial (NCT05043090), patients with be administered 600mg savolitinib (3 x 200mg tablets) once daily in combination with 1500mg durvalumab (administered intravenously (IV)) every four weeks.[1]

Key Innovation

PRCC is the most common subtype of non-clear cell renal cell carcinoma and has a poor prognosis, particularly in advanced stages and relatively few treatment options.[7,8] Since some cases of PRCC are driven by the MET gene, targeting MET may be a promising therapeutic approach. The combination of savolitinib and durvalumab has been shown to be tolerable, with a promising complete response rate in patients with MET-driven PRCC.[9,10] If licensed, savolitinib in combination with durvalumab will offer an additional treatment option for patients with unresectable and locally advanced or metastatic MET-driven PRCC.

Regulatory & Development Status

Savolitinib does not currently have Marketing Authorisation in the EU/UK for any indication.

Durvalumab as combination therapy currently has Marketing Authorisation in the EU/UK for the following indications: [6]

- In combination with etoposide and either carboplatin or cisplatin for the first-line treatment of adults with extensive-stage small cell lung cancer.
- In combination with gemcitabine and for the first line treatment of adults with locally advanced, unresectable, or metastatic biliary tract cancer.
- In combination with tremelimumab for the first line treatment of adults with advanced or unresectable hepatocellular carcinoma.

Durvalumab monotherapy currently has Marketing Authorisation in the EU/UK for non-small cell lung cancer (NSCLC).[6]

Savolitinib in combination with durvalumab is in phase III/II clinical development for NSCLC.[11]

Patient Group

Disease Area and Clinical Need

Renal cell cancer also called renal cell adenocarcinoma and the most common type of kidney cancer in adults. Around 80 out of 100 kidney cancers are renal cell cancers. Renal cell cancer starts in cells in one of the nephrons inside the kidney. Nephrons filter the blood and make urine. Each kidney has between 1 and 2 million nephrons.[12] PRCC is a cancer of the kidney tubes that filter waste products from the blood. PRCC makes up 15% of all renal cell carcinoma. There are two types of PRCC. Type 1 is more common and grows slowly. Type 2 is more aggressive and grows more quickly. Some people have symptoms with PRCC, but others don't. Symptoms can include: blood in the urine, pain, weight loss, tiredness, fever and a lump in the side.[13] Some known risk factors of PRCC include: smoking, obesity, hereditary leiomyomatosis, receiving dialysis treatment and hypertension.[14]

Although RCC represents only 2% of cancer diagnoses and deaths, its incidence has more than duplicated in developed regions in the past decades.[15,16] Kidney cancer is the sixth most common cancer in the UK, accounting for 4% of all new cancer cases (2017-2019). In females in the UK, kidney cancer is the 10th most common cancer (3% of all new female cancer cases). In males in the UK, it is the sixth most common cancer (4% of all new male cancer cases).[17] The estimated prevalence of MET-driven status is 35–40% in PRCC.[18] In England in 2023-2024, there were 31,943 finished consultation episodes (FCE) for malignant neoplasm of kidney, except renal pelvis (ICD-10 code C64), resulting in 19,171 day cases and 49,950 FCE bed days.[19]

Recommended Treatment Options

There is no treatment option recommended by NICE for unresectable and locally advanced or metastatic MET-driven PRCC.

NICE guidelines recommend the following combination treatment options for untreated advanced renal cell carcinoma: [20-23]

- Cabozantinib with nivolumab
- Lenvatinib with pembrolizumab
- Avelumab with axitinib
- Nivolumab with ipilimumab

NICE guidelines recommend the following monotherapy treatment options for untreated advanced renal cell carcinoma: [24-28]

- Cabozantinib
- Tivozanib
- Pazopanib
- Nivolumab
- Sunitinib

Clinical Trial Information

Trial	**SAMETA;** NCT05043090; 2021-000336-55; A Phase III, Open Label, Randomised, 3-Arm, Multi-Centre Study of The cost of savolitinib is not yet known. T Plus Durvalumab Versus Sunitinib and Durvalumab Monotherapy in MET-Driven, Unresectable and Locally Advanced or Metastatic Papillary Renal Cell Carcinoma **Phase III:** Recruiting **Location(s)**: Eight EU countries, UK, USA, Canada and other countries
Trial Design	Randomised, parallel assignment, open label
Population	N = 220 (estimated); histologically confirmed unresectable and locally advanced or metastatic PRCC.
Intervention(s)	Three 200mg Savolitinib oral tablets once daily 1500mg Durvalumab IV infusion every four weeks
Comparator(s)	Sunitinib capsules
Outcome(s)	Progression-Free Survival (PFS) /savolitinib plus durvalumab relative to sunitinib. Defined as time from randomisation until progression per RECIST 1.1 as assessed by blinded independent central review (BICR), or death due to any cause. [Time frame: Approximately 28 months post first subject randomised] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of savolitinib is not yet known.

The NHS indicative prices for 120mg per 2.4ml and 500mg per 10ml concentrate for solution for infusion vials of durvalumab are £592 and £2,466 respectively.[30]

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Cabozantinib with nivolumab for untreated advanced renal cell carcinoma (TA964). April 2024
- NICE technology appraisal. Lenvatinib with pembrolizumab for untreated advanced renal cell carcinoma (TA858). January 2023
- NICE technology appraisal. Nivolumab with ipilimumab for untreated advanced renal cell carcinoma (TA780). March 2022
- NICE technology appraisal. Avelumab with axitinib for untreated advanced renal cell carcinoma (TA645). September 2020

- NICE technology appraisal. Cabozantinib for untreated advanced renal cell carcinoma (TA542). October 2018
- NICE technology appraisal. Tivozanib for treating advanced renal cell carcinoma (TA512). March 2018
- NICE technology appraisal. Nivolumab for previously treated advanced renal cell carcinoma (TA417). November 2016
- NICE technology appraisal. Pazopanib for the first-line treatment of advanced renal cell carcinoma (TA215). February 2011
- NICE technology appraisal. Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma (TA169). March 2009
- NICE clinical guideline in development. Renal cell carcinoma Pathways Pilot (TA11186). Expected publication date to be confirmed

NHS England (Policy/Commissioning) Guidance

- 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). B01/S/a.

Other Guidance

- European Society for Medical Oncology (ESMO). Renal Cell Carcinoma Treatment Recommendations. 2021.[31]
- National Cancer Institute. Papillary Renal Cell Carcinoma. 2020.[32]

Additional Information

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