Innovation Observatory

NHS National Institute for Health Research

HEALTH TECHNOLOGY BRIEFING MARCH 2019

Savolitinib for MET-driven, unresectable and locally advanced or metastatic papillary renal cell carcinoma

NIHRIO ID	18303	**NICE ID**	10153
Developer/Company	AstraZeneca UK Ltd	**UKPS ID**	N/A

Licensing and market availability plans	Currently in phase III trial

SUMMARY

Savolitinib is a medicinal product that is currently in clinical development for the treatment of MET-driven, unresectable and locally advanced or metastatic papillary renal cell carcinoma. Renal cell carcinoma (RCC) is the most common type of kidney cancer and is described as locally advanced and metastatic when the cancer has spread from the kidneys to other parts of the body. Papillary RCC is a less common subtype of RCC and is associated with an inherited gene mutation ('MET-driven') that provides a potential target for emerging treatments. In most cases of advanced papillary RCC, surgery is not possible ('unresectable') and therapeutic options are often limited.

Savolitinib is a potent first-in-class, MET inhibitor that works by selectively inhibiting the MET-pathway which is responsible for the growth of the tumours in papillary RCC. Savolitinib is administered orally and early results from clinical studies suggests that it may suppress MET-driven tumour growth. If licensed savolitinib would offer a new treatment option for patients with MET-driven, unresectable and locally advanced or metastatic papillary renal cell carcinoma.

PROPOSED INDICATION

MET-driven, unresectable and locally advanced or metastatic papillary renal cell carcinoma (PRCC)[1]

TECHNOLOGY

DESCRIPTION

Savolitinib (AZD6094, HMPL-504, volitinib) is a potent, selective MET inhibitor.[2] It selectively binds to and inhibits the activation of c-Met in an ATP-competitive manner, and disrupts c-Met signal transduction pathways. This may result in cell growth inhibition in tumours that overexpress the c-Met protein. C-Met encodes the hepatocyte growth factor (HGF) receptor tyrosine kinase and plays an important role in tumour cell proliferation, survival, invasion, and metastasis, and tumour angiogenesis; this protein is overexpressed or mutated in a variety of cancers such as PRCC.[3]

Savolitinib is in clinical development for patients with MET-driven, unresectable and locally advanced or metastatic papillary renal cell carcinoma (PRCC). In the phase III clinical trial (SAVOIR; NCT03091192), savolitinib is administered orally at a dose of 600 mg (400 mg if <50 kg) with a meal once daily, continuously.[1]

INNOVATION AND/OR ADVANTAGES

Patients with advanced PRCC currently have limited therapeutic options. PRCC may involve activation of the MET pathway. The HGF receptor MET plays a central role in PRCC and aberrations, either through mutation, copy number gain, or trisomy of chromosome 7 occurring in the majority of cases. Savolitinib is a potent first-in-class, selective inhibitor of c-MET tyrosine kinase and results from a phase II clinical trial (NCT02127710) suggests that savolitinib may suppress MET-driven tumour growth.[2,4,5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

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

PATIENT GROUP

DISEASE BACKGROUND

Renal cell carcinoma (RCC) arises from renal epithelium. It is the most common form of kidney cancer.[6] In RCC, the cancerous cells start in the lining of the tubules (the smallest tubes inside the nephrons). The type of cancer depends on the type of cell the cancer starts in.[7] The most frequent RCC subtypes include clear cell, papillary [types 1 and 2] and chromophobe tumours. A recent characterisation of primary papillary renal cell carcinoma (PRCC) confirmed that type 1 and type 2 PRCC are not only clinically and pathologically diverse but also represent biologically different entities.[6]

MET pathway alterations are more characteristic of type 1 PRCC. Activation of the NRF2–antioxidant response elements (ARE) pathway, CDKN2A silencing, SETD2 mutations and TFE3 fusions are characteristics of type 2 PRCC. In type 1 PRCC, tumour development requires additional oncogenic events within the cell which is the rationale for a therapeutic strategy targeting MET pathway and its

regulators. The hereditary PRCC syndrome is an inherited condition that is associated with an increased risk of bilateral type 1 PRCC. The hereditary PRCC is due to mutation occurring in the gene MET and located on the chromosome 7.[6]

Patients with RCC can present with a range of symptoms; unfortunately, many patients are asymptomatic until the disease is advanced. At presentation, approximately 25% of individuals either have distant metastases or advanced locoregional disease. Patients with localised disease can present with a wide array of symptoms and/or laboratory abnormalities, or they may be diagnosed incidentally.[8] At present, the majority of RCCs are found incidentally from abdominal ultrasound or computer tomography examinations undertaken for various reasons. Significantly less frequent are visible signs and symptoms which most commonly include; microscopic or macroscopic haematuria, lateral dorsal or flank pain and palpable abdominal mass. RCC can become very large without any symptoms, due to the retroperitoneal position of the kidney. Paraneoplastic manifestations of RCC, including hypercalcaemia, production of adrenocorticotrophic hormone, polycythaemia, hepatic dysfunction, amyloidosis, fever and weight loss are present in up to 20% of patients.[9]

Several factors increase a person's risk of developing RCC, including age, genetics, family history, and exposure to risk factors (including some potentially avoidable lifestyle factors).lifestyle factors such as smoking increases the risk by 33%. Radiotherapy for cancers, certain occupational exposures, certain medical conditions such as thyroid cancer, high blood pressure, and diabetes and inadequate physical activity may relate to higher RCC risk.[10]

CLINICAL NEED AND BURDEN OF DISEASE

Kidney cancer was the seventh most common cancer in the UK in 2015 [11] The definition of kidney cancer includes cancers of the renal parenchyma (80%), the renal pelvis and the ureter.[7] Cancers of the renal parenchyma are also known as RCCs.[12] PRCC accounts for approximately 10% of renal parenchymal tumours.[13]

The incidence of kidney cancer was 12,547 new cases in England and Wales in 2015 with more than 4 in 10 cases diagnosed at a late stage in England (2014). Around 7,900 of these new cases were in males making it the 6th most common cancer in males. Incidence rates for kidney cancer are projected to rise by 26% in the UK between 2014 and 2035, to 32 cases per 100,000 people by 2035. An estimated 46,800 people who had previously been diagnosed with kidney cancer were alive in the UK at the end of 2010.

Almost 6 in 10 (56%) people diagnosed with kidney cancer in England and Wales survive their disease for five years or more while about half (50%) survive their disease for ten years or more. About 4500 deaths are due to kidney cancer in the UK yearly.[11] Five year survival estimates for 2011 to 2015 in RCC patients increased from 57.9% to 60.2% in men and from 60.1% to 62.0% in women. People diagnosed at the advanced stage (stage IV) died at more than twice the rate of the general population.[14]

Kidney cancer is rare in young adults and children, but rates begin to rise after the age of 40 years. About three quarters of people diagnosed with kidney cancer (75%) are over 60 years old and the highest rates are in the 70-74 years age range for men and 75-79 years age range for women. More than a third of cases (36%) were diagnosed in people aged over 75 years between 2013 and 2015.[12]

Hospital admissions data for England in 2017-2018 recorded 20,654 finished consultant episodes (FCE) for malignant neoplasm of kidney, except renal pelvis (ICD 10: C64), 17,520 hospital admissions and 8,170 day cases.[15]

With about 80% of kidney cancer being RCC,[7] and based on the incidence of 12,547 cases of kidney cancer in England and Wales in 2015, about 10,038 of these cases would be RCC. Metastases are known to occur in approximately 30% of cases of RCC,[16] and about 10% of RCC cases are PRCC.[13]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

While surgery is the main treatment for kidney cancer that has not spread to other parts of the body, targeted cancer drugs are one of the main treatment in advanced RCC. Some patients might benefit from surgery by having the kidney and/or the secondary cancer removed if they are well enough to recover from the operation. Other possible treatments include: freezing therapy (cryotherapy), radio wave treatment, radiotherapy, blocking the blood supply to the cancer (arterial embolisation), hormone therapy and chemotherapy.[17]

CURRENT TREATMENT OPTIONS

NICE guidelines recommends several therapies as first and second-line treatment in advanced RCC:[18]

Recommended first-line treatment options for metastatic RCC include the following;

- Cabozantinib for adults with untreated advanced renal cell carcinoma that is intermediate- or poor-risk as defined in the International Metastatic RCC Database Consortium criteria. It is recommended only if the company provides cabozantinib according to the commercial arrangement.
- Tivozanib as an option for treating advanced renal cell carcinoma in adults, only if:
  - they have had no previous treatment and
  - The company provides tivozanib with the discount agreed in the patient access scheme.
- Pazopanib is as a first-line treatment option for people with advanced RCC who have not received prior cytokine therapy and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and if the manufacturer provides pazopanib with a 12.5% discount on the list price as agreed in the patient access scheme.
- Sunitinib as a first-line treatment option for people with advanced and/or metastatic RCC who are suitable for immunotherapy and have an ECOG performance status of 0 or 1.

Recommended second-line treatment include the following;

- Lenvatinib plus everolimus for treating advanced renal cell carcinoma in adults who have had 1 previous VEGF-targeted therapy.
- Cabozantinib as an option for treating advanced renal cell carcinoma in adults after VEGF-targeted therapy
- Everolimus for treating advanced renal cell carcinoma that has progressed during or after treatment with vascular endothelial growth factor targeted therapy.
- Nivolumab as an option for previously treated advanced renal cell carcinoma in adults.
- Axitinib as an option for treating adults with advanced renal cell carcinoma after failure of treatment with a first-line tyrosine kinase inhibitor or a cytokine.

PLACE OF TECHNOLOGY

If licensed, savolitinib will offer an additional treatment option for patients with MET-driven, unresectable and locally advanced or metastatic papillary renal cell carcinoma.

CLINICAL TRIAL INFORMATION

Trial	SAVOIR, NCT03091192, ; savolitinib vs sunitinib; phase III
Sponsor	AstraZeneca
Status	Ongoing
Source of Information	Trial registry[1], journal article[2]
Location	2 EU countries (not UK), USA, Russia, Ukraine, Brazil and Republic of Korea,
Design	Randomised, controlled, parallel assignment, open label.
Participants	N=60; aged 18-130 years; histologically confirmed PRCC, which is unresectable/locally advanced or metastatic with measurable disease as per RECIST 1; confirmation of MET-driven PRCC without co-occurring fumarate hydratase (FH) or von-Hippel Lindau (VHL) mutations from an FFPE tumour sample using the sponsor-designated central laboratory validated NGS assay; patients who have received no prior systemic therapy as well as those who have received prior systemic therapy for PRCC in the advanced setting; adequate haematological, renal, cardiac and liver functions; karnofsky performance status ≥ 80
Schedule	Randomised to savolitinib 600 mg (400 mg if <50 kg) by mouth with a meal once daily, continuously; or sunitinib 50 mg by mouth once daily, with or w/o food, 4 weeks on/2weeks off.
Follow-up	Time from randomisation to progression or death
Primary Outcomes	Progression Free Survival (PFS) [Time frame: up to approximately 32 months after 1st patient randomised (121 PFS occurrences)]
Secondary Outcomes	• Overall Survival (OS) [Time frame: Up to approximately 47 months after 1st patient randomized (121 OS occurrences)] • Objective Response Rate (ORR) [Time frame: Up to approximately 32 months after 1st patient randomized (at the time of PFS analysis)] • Duration of Response (DoR) [Time frame: Up to approximately 32 months after 1st patient randomized (at the time of PFS analysis)] • Disease Control Rate (DCR) [Time frame: At 6 and 12 months following the date of randomisation] • The plasma concentration-time data will be analysed by non-linear mixed effects modelling in order to evaluate the pharmacokinetic characteristics of savolitinib [Time frame: cycle 1 day 1 - pre-dose; cycle 1 day 15 - pre-dose and 1 and 3 hours post-dose; cycle 1 day 29 - pre-dose; cycle 2 day 15 - pre-dose] • Mean change from baseline in FKSI-19 (cancer therapy kidney symptom index-19) score [Time frame: From date of randomization until the date of first documented progression, date of death from any cause, or end of treatment, whichever came first, assessed up to approximately 32 months] • Mean change from baseline in FACIT-F (Functional Assessment of Chronic Illness Therapy - Fatigue) score [Time frame: From date of randomization until the date of first documented progression, date of death from any cause, or end of treatment, whichever came first, assessed up to approximately 32 months] • Best percentage change in tumour size [Time frame: Up to approximately 32 months after 1st patient randomized (at the time of PFS analysis)]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date reported as August 2019

ESTIMATED COST

The cost of savolitinib is not yet known.

ADDITIONAL INFORMATION

AstraZeneca UK Ltd did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Atezolizumab plus bevacizumab for untreated locally advanced or metastatic renal cell carcinoma (ID1365). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Pembrolizumab with axitinib for untreated metastatic renal cell carcinoma (ID1426). Expected May 2020.
- NICE technology appraisal in development. Nivolumab with ipilimumab for untreated metastatic renal cell carcinoma (ID1182). Expected April 2019.
- 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. Pazopanib for the first-line treatment of advanced renal cell carcinoma (TA215). August 2013.
- NICE technology appraisal. Bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (secondibndfirstaptemsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma (TA178). August 2009.
- NICE technology appraisal. Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma (TA169). March 2009.
- NICE interventional procedure guidance. Irreversible electroporation for treating renal cancer (IPG443). February 2013.
- NICE interventional procedure guidance. Laparoscopic cryotherapy for renal cancer (IPG405). August 2011.
- NICE interventional procedure guidance. Percutaneous cryotherapy for renal cancer (IPG402). July 2011.
- NICE interventional procedure guidance. Percutaneous radiofrequency ablation for renal cancer (IPG353). July 2010.
- NICE interventional procedure guidance. Laparoscopic partial nephrectomy (IPG151). January 2006.
- NICE interventional procedure guidance. Laparoscopic nephrectomy (including nephroureterectomy) (IPG136). August 2005

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.
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OTHER GUIDANCE

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- European Association of Urology (EAU). Updated European Association of Urology Guidelines: Recommendations for the Treatment of First-line Metastatic Clear Cell Renal Cancer. 2018.[20]
- National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Kidney Cancer. Version 2. 2017.[21]
- European Association of Urology. European Association of Urology (EAU) Guidelines on Renal Cell Carcinoma.2016.[22]
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