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HEALTH TECHNOLOGY BRIEFING JANUARY 2020

Lenvatinib in addition to everolimus or pembrolizumab for advanced renal cell carcinoma – First line

NIHRIO ID	13252	**NICE ID**	10114
Developer/Company	Eisai Ltd	**UKPS ID**	642914

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

The addition of lenvatinib to everolimus or pembrolizumab is in clinical development for the first line treatment of advanced renal cell carcinoma (RCC). RCC is the most common form of cancer that originates in the kidney. It may occur due to the mutation of cells in the kidney's filtering system. RCC often has few symptoms, so may be diagnosed in advanced stages, when the cancer has spread to other organs. While current treatments exist for advanced RCC, significant unmet medical need remains for more effective treatment options with manageable safety profiles for patients in the first-line setting.

Lenvatinib is a tyrosine kinase inhibitor that targets several different growth factor receptors including vascular endothelial growth factor (VEGFR) and fibroblast growth factor receptors (FGFR). By blocking these receptors lenvatinib can reduce tumour growth in the kidney. Lenvatinib, everolimus and pembrolizumab are already used for advanced RCC in various combinations and clinical settings. The addition of lenvatinib to everolimus or pembrolizumab has shown potential to be more effective than each drug on its own in improving outcomes for advanced RCC patients and will offer an additional option as a first-line treatment.

PROPOSED INDICATION

First-line treatment for advanced renal cell carcinoma.[1]

TECHNOLOGY

DESCRIPTION

Lenvatinib (Kisplyx) is a multiple receptor tyrosine kinase (RTK) inhibitor with a novel binding mode that selectively inhibits the kinase activities of all vascular endothelial growth factor receptors (VEGFR), in addition to other proangiogenic and oncogenic pathway-related RTKs including all fibroblast growth factor receptors (FGFR), the platelet-derived growth factor (PDGF) receptor PDGFRα, KIT and RET that are involved in tumour proliferation. Lenvatinib is potentially the first TKI that simultaneously inhibits the kinase activities of FGFR as well as these other cancer-related RTKs.[2]

Lenvatinib in addition to everolimus or pembrolizumab is in clinical development for first-line treatment of patients with advanced RCC. In phase III clinical trial (NCT02811861, CLEAR), participants received either; 18 mg lenvatinib and 5 mg everolimus, both administered orally once a day, or 20 mg lenvatinib administered orally once a day and 200 mg pembrolizumab intravenously every 3 weeks.[1]

INNOVATION AND/OR ADVANTAGES

Lenvatinib, everolimus and pembrolizumab are already used in various combinations and clinical settings but significant unmet medical need remains for more effective treatment options with manageable safety profiles for patients in the first-line setting.

Lenvatinib in combination with everolimus is approved for the treatment of patients with advanced RCC in the second-line setting with studies showing increased anti- angiogenic and anti-tumour activity as demonstrated by decreased human endothelial cell proliferation, tube formation, and VEGF signalling in vitro and tumour volume in mouse xenograft models of human renal cell cancer greater than each drug alone.[3]

Similarly lenvatinib plus pembrolizumab demonstrated promising antitumor activity in a phase I/II trial of renal cell cancer in addition to preclinical studies demonstrating greater antitumor activity than either agent alone and was accompanied by an improved immune response, likely mediated by CD8+ T cells.[3]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Lenvatinib mesilate (Kispylx) is currently licenced in combination with everolimus in the UK for the treatment of:[4]

- advanced renal cell carcinoma following one prior vascular endothelial growth factor (VEGF)-targeted therapy.

Very common adverse events (occurs in 1 in 10 patients) of lenvatinib are: urinary tract infection, hypothyroidism, hypocalcaemia, thrombocytopenia, decreased weight and appetite, insomnia, headache, dysgeusia, dizziness, hypertension, haemorrhage, diarrhoea, vomiting, oral pain and inflammation, constipation, dyspepsia, dysphonia, dry mouth, rash, alopecia, pain, palmar erythema, palmar-plantar erythrodysaesthesia syndrome, myalgia, proteinuria, arthralgia, oedema peripheral, fatigue and asthenia.[5]

Lenvatinib plus pembrolizumab was given FDA breakthrough therapy designation for renal cancer in January 2018.[6]

Lenvatinib plus pembrolizumab is in phase III clinical development for malignant melanoma, head and neck squamous cell carcinoma, hepatocellular carcinoma, non-small cell lung cancer, endometrial and urothelial cancer. This combination is also in phase II clinical development for advanced solid tumours like gastric, thyroid and breast cancer.[7]

Lenvatinib plus everolimus is in phase II clinical development for thyroid cancer and advanced carcinoid tumours.[8]

PATIENT GROUP

DISEASE BACKGROUND

Renal cell cancer (RCC) is the most common type of kidney cancer in adults. RCC starts in the lining of the tubules (the smallest tubes of the nephrons of the kidneys) which filter blood and make urine. There are several types of RCC depending on the type of cell in which the cancer originates, including: clear cell RCC (75% of RCCs), papillary (10% of RCCs) and chromophobe (5% of RCCs). The remaining types of RCC comprise of rare carcinomas of the collecting ducts and renal medullary carcinoma.[9] In advanced RCC the cancer has spread away from the kidney and is usually graded at stage IV.[10]

Several factors increase a person's risk of developing RCC including age, genetics, family history, and exposure to other risk factors (including some potentially avoidable lifestyle factors). Lifestyle factors such as smoking increases 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 also relate to higher RCC risk.[11]

Patients with RCC can present with a range of symptoms including blood in the urine but unfortunately, many patients are asymptomatic until the disease is advanced.[12] At presentation, approximately 25% of individuals either have distant metastases or advanced loco regional disease.[13] 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.[14] Living with RCC may also impact emotions and relationships, causing anxiety, fear and depression for the patient and relatives and friends.[15]

CLINICAL NEED AND BURDEN OF DISEASE

Kidney cancer was the 7th most common cancer in the UK in 2015 with more than 4 in 10 cases diagnosed at a late stage in England (2014). [16] According to the Office of National Statistics the incidence of kidney cancer was 9,298 new cases in England in 2017 (ICD-10 code C64).[17] 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.[18]

Hospital admission data for England in 2018-19 recorded 20,866 finished consultant episodes (FCE), 17,674 hospital admissions and 8,510 day cases for malignant neoplasm of kidney, except renal pelvis (ICD 10: C64).[19]

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 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.[16]

In 2017, kidney cancer was the 13th most common cause of cancer death in the UK accounting for 3% of all cancer deaths.[18] The Office of National Statistics reported in 2017 that the 1 year age-standardised survival for RCC was 79.3% overall and 38.7% for those diagnosed at stage IV. The 5 year age-standardised survival was 63.8%, 12.4% for those diagnosed at stage IV.[20] In 2018 there were 3,554 registrations of death from cancer for malignant neoplasm of kidney, except renal pelvis in England (ICD-10 code C64).[21]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

There are currently no treatments that reliably cure advanced RCC. The primary objectives of medical intervention are relief of physical symptoms and maintenance of function.[22]

Metastasectomy and other local treatment strategies including whole-brain radiotherapy, conventional radiotherapy, stereotactic radiosurgery, stereotactic body radiotherapy, CyberKnife® radiotherapy and hypofractionated radiotherapy can be considered and carried out for selected patients after multidisciplinary review.[23] Other possible treatments include cyrotherapy and arterial embolization.[10]

CURRENT TREATMENT OPTIONS

According to NICE guidelines, current first-line treatment options for people with advanced and/or metastatic renal cell carcinoma who are suitable for immunotherapy and have an ECOG performance status of 0 or 1 include:[24]

- Pazopanib
- Sunitinib

Recommended treatment options for adults with untreated advanced renal cell carcinoma that is intermediate- or poor-risk as defined in the International Metastatic Renal Cell Carcinoma Database Consortium criteria include:[24]

- Nivolumab with ipilimumab (recommended for use within the Cancer Drugs Fund)
- Cabozantinib

Tivozanib is recommended as an option for treating advanced renal cell carcinoma in adults, only if they have had no previous treatment.[24]

PLACE OF TECHNOLOGY

If licensed, lenvatinib in combination with everolimus or pembrolizumab would provide an additional option for the first-line treatment of advanced untreated renal cell carcinoma.

CLINICAL TRIAL INFORMATION

Trial	**CLEAR, NCT02811861, KEYNOTE-581, 2016-000916-14 ; adults aged ≥18 years; lenvatinib with everolimus or pembrolizumab vs sunitinib; phase III.**
Sponsor	Eisai Inc

Status	Ongoing
Source of Information	Trial registry[1,25]
Location	EU (incl UK), USA, Canada and other countries.
Design	Randomised, open label, active-comparator.
Participants	N = 1069 (planned); adults aged ≥18 years; renal cell carcinoma with a clear-cell component; who have not received any systemic anticancer therapy for RCC.
Schedule	Participants were randomised to receive: - Lenvatinib 18 milligrams (mg) administered orally, once daily, plus everolimus 5 mg administered orally, once daily - Lenvatinib 20 mg administered orally, once daily, plus pembrolizumab 200 mg administered intravenously (IV), every 3 weeks - Sunitinib 50 mg administered orally, once daily, on a schedule of 4 weeks on treatment followed by 2 weeks off treatment.
Follow-up	Up to 53 months.
Primary Outcomes	• Progression-free survival (PFS) by independent review [Time Frame: up to 43 months approximately]
Secondary Outcomes	• Objective response rate (ORR) [Time frame: up to approximately 53 months] • Overall survival (OS) [Time frame: up to approximately 53 months] • Number of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) [Time frame: up to approximately 53 months] • Number of participants who discontinued treatment due to toxicity [Time frame: up to approximately 53 months] • Time to treatment failure due to toxicity [Time frame: up to approximately 53 months] • Health-Related Quality of Life (HRQoL) scores [Time frame: up to approximately 53 months] • PFS on next-line of therapy (PFS2) [Time frame: up to approximately 53 months] • PFS by investigator assessment [Time frame: up to 53 Months approximately] • Model-predicted clearance for lenvatinib and everolimus [Time frame: 0.5-4 hours (h) and 6-10h postdose on Cycle 1 Day 1; predose and 2-12h postdose on Cycle 1 Day 15; predose and 0.5-4 h and 6-10h postdose on Cycle 2 Day 1; predose on Day 1 of Cycles 3, 4, 5, and 6] • AUC for lenvatinib and everolimus [Time frame: 0.5-4h and 6-10h postdose on Cycle 1 day 1; predose and 2-12h postdose on Cycle 1 fay 15; predose and 0.5-4h and 6-10h postdose on Cycle 2 day 1; predose on day 1 of Cycles 3, 4, 5, and 6]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion date reported as February 2021.

Trial	NCT02501096, 2017-000300-26, **E7080-A001-111; adults aged ≥18 years; lenvatinib with pembrolizumab; phase I/II.**
Sponsor	Eisai Inc
Status	Ongoing
Source of Information	Trial registry[26,27]
Location	United States, Spain and Norway.
Design	Single group assignment.
Participants	N = 357 (planned); adults aged ≥18 years; renal cell carcinoma; progressed on treatment with anti-PD-1/PD-L1 mAb.
Schedule	Participants receive lenvatinib 20 mg/day orally and pembrolizumab 200 mg intravenously every 3 weeks.
Follow-up	Up to 2 years.
Primary Outcomes	• Maximum Tolerated Dose (Phase 1b) [Time Frame: Cycle 1] • Objective response rate (ORR) at Week 24 • Dose Limiting Toxicity (Phase 1b) [Time Frame: Cycle 1]
Secondary Outcomes	• Number of participants with treatment emergent adverse events (TEAEs) and treatment emergent serious adverse events (SAEs) [Time Frame: For each participant, from the first dose till 90 days after the last dose, unless participant starts new anticancer drug then 30 days, or up to approximately 2 years] • ORR [Time Frame: up to approximately 2 years] • Progression-free survival (PFS) [Time Frame: From the date of first dose of study drug to the date of first documentation of confirmed disease progression or death (whichever occurs first) or up to approximately 2 years] • Overall survival (OS) [Time Frame: up to approximately 2 years] • Duration of response (DOR) [Time Frame: up to approximately 2 years] • Disease control rate (DCR) [Time Frame: up to approximately 2 years] • Durable stable disease rate (DSDR) [Time Frame: up to approximately 2 years] • Clinical benefit rate (CBR) [Time Frame: up to approximately 2 years] • Area under the curve (AUC) of lenvatinib [Time Frame: 0.5-4 hours (hrs), and 6-10 hrs post lenvatinib dose on C1D1, pre-dose, 0.5-4 hrs, and 6-10 hrs post lenvatinib dose on C1D15, and pre-pembrolizumab dose and 2-12 hrs post lenvatinib dose on C2D1. Pre-pembrolizumab dose only on Day 1 of Cycles 3 to 6.] • Apparent clearance of lenvatinib
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion date reported as April 2020.

ESTIMATED COST

Lenvatinib is already marketed in the UK; 30 x 4 mg or 10mg capsules cost £1,437.00[28]

Everolimus is already marketed in the UK; 30 x 5mg tablets cost £2,250.00[29]

Pembrolizumab is already marketed in the UK; a 100mg/4ml concentrate for solution for infusion vials costs £2,630.00, a 50mg powder for concentrate for solution for infusion vials for £1,315.00[30]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Avelumab with axitinib for untreated advanced or metastatic renal cell carcinoma (ID1547). Expected publication April 2020.
- NICE technology appraisal in development. Pembrolizumab with axitinib for untreated metastatic renal cell carcinoma (ID1426). Expected publication May 2020.
- NICE technology appraisal in development. Nivolumab with ipilimumab for untreated advanced renal cell carcinoma (TA581). May 2019.
- NICE technology appraisal. Cabozantinib for untreated advanced renal cell carcinoma (TA542). October 2018.
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- 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 cancer service guideline. Improving outcomes in urological cancers (CSG2). September 2002.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- 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. Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2019[23]

ADDITIONAL INFORMATION

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