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Newcastle University

Health Technology Briefing
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Belzutifan with Lenvatinib in Patients with Advanced Renal Cell Carcinoma

Company/Developer	Merck Sharp & Dohme Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 30655	NICE ID: Not available	UKPS ID: 674305

Licensing and Market Availability Plans

Currently in phase lll clinical development.

Summary

Belzutifan in combination with lenvatinib are in clinical development for the treatment of adults with advanced clear cell renal cell carcinoma (RCC) after previous treatment. Clear cell RCC is the most common type of kidney cancer and is named after how the tumour looks under the microscope. Because early-stage RCC often goes undetected, approximately 16% of patients present with advanced RCC, which is defined as stage IV disease that may or may not include metastasis. Most patients with RCC are usually asymptomatic in the early stage, but symptoms that appear as the cancer progresses, includes blood in the urine, anaemia (not enough healthy red blood cells), flank pain, weight loss and fatigue. Treatment options for RCC in the late-line setting after previous treatments are limited.

Belzutifan is a first-in-class drug that works by selectively blocking the activity of a protein called HIF-2α, which plays a role in cell survival, cell growth and blood vessel formation. It is being used together with lenvatinib which blocks the activity of enzymes known as tyrosine kinases, which stop the formation of new blood vessels and cuts off the growth supply to the cancer cells. If licensed, belzutifan in combination with lenvatinib (administered orally) would offer an additional treatment option for patients who have previously received treatment for advanced RCC.

Proposed Indication

Treatment of advanced renal cell carcinoma (RCC) who have progressed after prior anti-PD-1/PD-L1 therapy.[1]

Technology

Description

Belzutifan (MK-6482, PT2977, WELIREG)[1] is a first-in-class oral drug that works by selectively blocking the activity of a protein called hypoxia inducible factor (HIF)-2α. This protein accumulates when the oxygen levels in cells are low, enabling the body to adjust to hypoxia.[2] Under normal oxygen levels, HIF-2α is targeted for ubiquitin-proteasomal degradation by VHL protein. Lack of functional VHL protein results in stabilisation and accumulation of HIF-2α. Upon stabilisation, HIF-2α translocates into the nucleus and interacts with hypoxia-inducible factor 1 beta (HIF-1b) to form a transcriptional complex that regulates expression of downstream genes, including genes associated with cellular proliferation, angiogenesis, and tumour growth (including CCND1, VEGFA, SLC2A1 (GLUT1), IGFBP3, TGFa, AXL, CXCR4, IL6). Belzutifan binds to HIF-2α, and in conditions of hypoxia or impairment of VHL protein function, belzutifan blocks the HIF-2α -HIF-1b interaction, leading to reduced transcription and expression of HIF-2α target genes.[3] HIF-2α also regulates VEGF expression and is involved in resistance to anti-VEGF therapy.[4]
The combination of belzutifan and lenvatinib is currently in clinical development for the treatment of adult and older adult patients with advanced RCC (aRCC) with clear cell component after prior therapy. In the phase III clinical trial (NCT04586231), participants were administered belzutifan 120 mg and lenvatinib 20 mg orally once a day. [1]

Key Innovation

Treatment options for RCC in the late-line setting after immunotherapy and VEGF-targeted therapy are limited.[5] Furthermore, no standard-of-care has been established based on randomised and controlled phase III studies for patients with advanced clear cell RCC that have progressed after anti-PD-1/PD-L1-based therapy.[4] Belzutifan, a first-in-class HIF-2α inhibitor, showed promising antitumor activity in a cohort of heavily pretreated RCC patients.[5] Through the combination of the belzutifan and the VEGF inhibitor lenvatinib, it has been demonstrated that belzutifan can suppress the transcriptional regulation of VEGF by HIF-2α, while lenvatinib inhibits the production of VEGF downstream of HIF-1α at the receptor level. In addition, as HIF-2α drives tumour cell expression of several oncogenes in clear cell RCC, VEGF being just one of them, the combination could inhibit multiple oncogenic signalling pathways involved in initiation, progression and metastasis.[4] The combination of belzutifan and lenvatinib indicated promising clinical activity with manageable toxicity in patients with advanced clear cell renal cell carcinoma (ccRCC) and disease progression after receiving a PD-1/L1 inhibitor and a VEGF-TKI.[6] Lenvatinib inhibits the kinase activities of VEGF receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4). In addition, lenvatinib inhibits FGF receptors FGFR1, 2, 3, and 4; PDGFRα; KIT; and RET. This inhibition results in the arrest of the neo-vessel assembly and maturation, decreasing vascular permeability of the tumour microenvironment.[7]

If licensed, belzutifan will offer an additional treatment option for adult patients with advanced RCC with clear cell component after anti-PD-1/PD-L1 therapy.

Regulatory & Development Status

As a monotherapy, belzutifan has Marketing Authorisation in the UK for the treatment of adult patients with von Hippel-Lindau (VHL) disease who require therapy for: [3,8]

- VHL associated renal cell carcinoma (RCC)
- central nervous system (CNS) hemangioblastomas
- pancreatic neuroendocrine tumours (pNET)
- for whom localised procedures are unsuitable or undesirable.

Lenvatinib has Marketing Authorisation in the UK for the treatment of adult patients with advanced renal cell carcinoma (RCC): [9]

- in combination with pembrolizumab, as first-line treatment.
- in combination with everolimus, following one prior vascular endothelial growth factor (VEGF)-targeted therapy.

Belzutifan has the following regulatory designations/awards: [10]

- an orphan drug designation by the European Medicines Agency (EMA) in August 2020 for the treatment of von Hippel-Lindau (VHL) disease-associated clear cell RCC.

Belzutifan is currently in phase II and III clinical development for the treatment of:[11]

- Advanced pheochromocytoma/paraganglioma, pancreatic neuroendocrine tumour, von Hippek-Lindau disease-associated tumours, advanced gastrointestinal stromal tumour, or solid tumours with HIF-2α related genetic alterations
- Solid tumours in combination with pembrolizumab and lenvatinib
- ccRCC in combination with cabozantinib
- ccRCC post nephrectomy in combination with pembrolizumab

Patient Group

Disease Area and Clinical Need

Clear cell RCC is the most common type of kidney cancer, comprising 75% of all kidney tumours.[12,13] In RCC, the cancerous cells start in the lining of the tubules which help to filter blood and make urine.[14] Clear cell renal cell carcinoma is named as such because when the tumour is viewed under the microscope, the cells in the tumour look clear.[15] Most patients with early-stage RCCs are asymptomatic; patients become symptomatic when the tumour has reached a late stage and/or metastases are present. Haematuria (blood in the urine) is the most common presenting symptom, other symptoms include anaemia, flank pain, palpable renal mass, weight loss, fatigue, night sweats and fever.[16] Some risk factors for RCC include smoking, kidney disease, being overweight, faulty genes and inherited conditions, and family history of kidney cancer. [16] Locally advanced cancer is when the cancer has grown larger but has not spread to other parts of the body, whereas metastatic cancers have spread from the area of origin to other parts of the body. These often cannot be cured but can be managed with treatment.[17]

Clear cell RCC accounts for 75% of RCC cases.[18] In England (2017), there were 51,041 patients diagnosed with Kidney and Urinary Tract cancer. For patients diagnosed between 2013 and 2017, followed up to 2018, the age-standardised 1-year and 5-year survival rates were 78.3% and 61.1% respectively.[19] In England in 2022-2023, there were 29,076 finished consultant episodes (FCE) and 26,274 hospital admissions for malignant neoplasm of kidney, except renal pelvis (ICD-10 code C64) which resulted in 49,389 FCE bed days and 16,963 day cases.[20]

Recommended Treatment Options
NICE recommends the following targeted pharmacological treatment options for previously treated advanced RCC. None of the treatment options below are specific to clear cell RCC:[21-25] • Cabozantinib for treating advanced RCC in adults after vascular endothelial growth factor (VEGF)-targeted therapy • Nivolumab for previously treated advanced renal cell carcinoma • Lenvatinib with everolimus for previously treated advanced renal cell carcinoma • Axitinib for treating advanced renal cell carcinoma after failure of prior systemic treatment

Clinical Trial Information	
Trial	NCT04586231, 2020-002075-35; An Open-label, Randomized, Phase 3 Study of MK-6482 in Combination With Lenvatinib (MK-7902) vs Cabozantinib in Participants With Advanced Renal Cell Carcinoma Who Have Progressed After Prior Anti-PD-1/L1 Therapy **Phase III –** Active, not recruiting **Location(s):** Thirteen EU countries, UK, USA, Canada, and other countries **Primary completion date:** December 2024
Trial Design	Randomised, open label, parallel assignment
Population	N=708 (estimated); aged 18 years and older; subjects with unresectable, locally advanced or metastatic clear cell RCC, disease progression on or after an anti-programmed cell death-1/ligand 1 (PD-1/L1) therapy as either first or second-line treatment for locally advanced/metastatic RCC or as adjuvant treatment or neoadjuvant/adjuvant with progression on or within 6 months of last dose.
Intervention(s)	Experimental arm includes belzutifan + lenvatinib: ○ Belzutifan 120 mg and lenvatinib 20 mg orally once a day
Comparator(s)	Cabozantinib 60 mg orally once a day
Outcome(s)	Primary outcome measure: • Progression-Free Survival (PFS) per Response Evaluation Criteria in Solid tumours Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR) [Time frame: Up to approximately 34 months] • Overall Survival (OS) [Time frame: Up to approximately 44 months] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The list price for a 90-tablet pack of 40 mg belzutifan is £11,936.70.[26]

The price of lenvatinib is £1,437 per 30 capsules (4 mg or 10 mg).[27]

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Subcutaneous nivolumab for treating advanced renal cell carcinoma after systemic treatment (ID 12008). TBC.
- NICE technology appraisal in development. Nivolumab with ipilimumab for adjuvant treatment of localised renal cell carcinoma (ID 9659). TBC.
- NICE technology appraisal in development. Cabozantinib with nivolumab and ipilimumab for untreated intermediate- or poor-risk advanced renal cell carcinoma (ID 6330). TBC.
- NICE technology appraisal guidance. Lenvatinib with everolimus for previously treated advanced renal cell carcinoma (TA498). January 2018.
- NICE technology appraisal guidance. Cabozantinib for previously treated advanced renal cell carcinoma (TA463). August 2017.
- NICE technology appraisal guidance. Everolimus for advanced renal cell carcinoma after previous treatment (TA432). February 2017.
- NICE technology appraisal guidance. Nivolumab for previously treated advanced renal cell carcinoma (TA417). November 2016.
- NICE technology appraisal guidance. Axitinib for treating advanced renal cell carcinoma after failure of prior systemic treatment (TA333). February 2015.

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). ESMO Clinical Practice Guideline update on the use of immunotherapy in early stage and advanced renal cell carcinoma. 2021.[28]
- European Society for Medical Oncology (ESMO). Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. 2019.[29]

Additional Information

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