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Newcastle University

# Health Technology Briefing
# June 2022

# Belzutifan for advanced or metastatic clear cell renal cell carcinoma after 1 therapy

| Company/Developer | Merck Sharp & Dohme Ltd |
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☐ New Active Substance ☒ Significant Licence Extension (SLE)

| NIHRIO ID: 27251 | NICE ID: 11767 | UKPS ID: 665441 |
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## Licensing and Market Availability Plans

Currently in phase III clinical trials.

## Summary

Belzutifan is currently in clinical development for the treatment of adult patients with advanced or metastatic clear cell renal cell carcinoma (ccRCC) after previous treatment. ccRCC is the most common type of kidney cancer and is called as such because the cancer cells appear clear when viewed under a microscope. Most patients with renal cell carcinomas (RCC) are usually asymptomatic in the early stage, but symptoms appear as the cancer progresses, which includes blood in the urine, anaemia (not enough healthy red blood cells), flank pain, weight loss and fatigue. Locally advanced cancer is when the cancer has grown outside the body part it started, whereas metastatic cancers have spread to other parts of the body. Treatment options for RCC in the late-line setting after previous treatments are limited.

Belzutifan is a first-in-class drug that is administered orally and 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. HIF-2α is considered a target for the treatment of ccRCC. By blocking HIF-2α, belzutifan will slow down the worsening of ccRCC and improve symptoms. If licensed, belzutifan would offer an additional treatment option for patients who have previously received treatment for locally advanced or metastatic ccRCC.

## Proposed Indication

For the second line treatment of adult patients with locally advanced or metastatic clear cell renal cell carcinoma (ccRCC) that has progressed after prior systemic treatment with Programmed cell death 1 ligand 1 (PD-1/L1) checkpoint inhibitor and a vascular endothelial growth factor - tyrosine kinase inhibitor (VEGF-TKI) in sequence or in combination.[1]

## Technology

### Description

Belzutifan (MK-6482, PT2977, WELIREG) is a first-in-class oral drug that works by selectively blocking the activity of a protein called hypoxia inducible factor (HIF)-2α, which accumulates when the oxygen levels in cells are low, enabling the body to adjust to hypoxia and grow more red blood cells and new blood vessels in response to the shortage of oxygen.[2,3] (HIF)-2α is a transcription factor that has been established as an oncogenic driver in ccRCC.[4]

Belzutifan is currently in clinical development for the second line treatment of adult patients with advanced ccRCC that has progressed after prior PD-1/L1 and VEGF-targeted therapies. In the phase III clinical trial (MK-6482-005, NCT04195750), participants are given 120mg belzutifan oral tablet once daily.[1]

### Key Innovation

Treatment options for RCC in the late-line setting after immunotherapy and VEGF-target therapy are limited. Belzutifan recently showed promising antitumor activity in a cohort of heavily pretreated ccRCC patients.[4] Belzutifan offers a novel approach to treating RCC, taking a different path than commonly used VEGF-TKIs or checkpoint inhibitors, which are used in various combinations to treat metastatic ccRCC. Belzutifan is highly selective and as a result, hypoxic signalling in cancer cells is impaired, blocking the transcription of several genes involved in cancer cell growth, proliferation, and abnormal blood vessel formation.[5]

If licenced, belzutifan would offer an additional treatment option for patients with locally advanced or metastatic ccRCC that has progressed after prior treatment.

### Regulatory & Development Status

Belzutifan has Marketing Authorisation in the UK for the treatment of adult patients with von Hippel-Lindau (VHL) disease who require therapy for VHL associated renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastomas, or pancreatic neuroendocrine tumours (pNET), and for whom localised procedures are unsuitable or undesirable.[6]

Belzutifan is in phase II clinical development for the treatment of pheochromocytoma/paraganglioma, pancreatic neuroendocrine tumour, and multiple solid tumours.[7]

## Patient Group

### Disease Area and Clinical Need

Clear cell renal cell carcinoma (ccRCC) is the most common type of kidney cancer, comprising 75% of all kidney tumours.[8] In RCC, the cancerous cells start in the lining of the tubules which help to filter blood and make urine.[9] ccRCC is named as such because when the tumour is viewed under the microscope, the cells

in the tumour look clear.[10] 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 is the most common presenting symptom, other symptoms include anaemia, flank pain, palpable renal mass, weight loss, fatigue, night sweats and fever.[11] Some risk factors for RCC include smoking, kidney disease, being overweight, faulty genes and inherited conditions, and family history of kidney cancer.[12] 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.[13]

In England in 2020-21, there were 20,380 finished consultant episodes (FCE) and 17,908 admissions for malignant neoplasm of kidney, except renal pelvis (ICD-10 code C64), resulting in 38,608 FCE bed days and 9,984 day cases.[14] There are no overall UK-wide statistics available for the different stages of kidney cancer, however for people diagnosed with kidney cancer (including ccRCC) in England between 2013-17:[15]

- Around 80% survive 1 year or more after diagnosis
- Around 65% survive 5 years or more after diagnosis
- More than 50% survive 10 years or more after diagnosis

## Recommended Treatment Options

NICE recommends the following targeted pharmacological treatment options for previously treated advanced RCC:[16-20]

- Axitinib
- Nivolumab
- Everolimus
- Cabozantinib
- Lenvatinib with everolimus

## Clinical Trial Information

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| Trial | **MK-6482-005; NCT04195750; 2019-003444-72;** An Open-label, Randomized Phase 3 Study of MK-6482 Versus Everolimus in Participants With Advanced Renal Cell Carcinoma That Has Progressed After Prior PD-1/L1 and VEGF-Targeted Therapies<br>**Phase III –** Active, not recruiting<br>**Location(s):** 9 EU countries, UK, USA, Canada and other countries<br>**Primary completion date:** September 2025 |
| Trial Design | Randomised, open label, parallel assignment. |
| Population | N=736 (estimated); aged 18 years and older; Subjects with unresectable, locally advanced or metastatic clear cell renal cell carcinoma (RCC) that have had disease progression on or after having received systemic treatment for locally advanced or metastatic RCC with both Programmed cell death 1 ligand 1 (PD-1/L1) checkpoint inhibitor and a vascular endothelial growth factor - tyrosine kinase inhibitor (VEGF-TKI) in sequence or in combination |
| Intervention(s) | 120mg of belzutifan (oral) once daily |
| Comparator(s) | 10mg of everolimus (oral) once daily |

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| Outcome(s) | • Progression-free Survival (PFS) per Response Criteria in Solid Tumors Version 1.1 (RECIST 1.1) [ Time Frame: Up to approximately 47 months]<br>• Overall Survival (OS) [ Time Frame: Up to approximately 47 months]<br><br>See trial record for full list of other outcomes. |
| Results (efficacy) | - |
| Results (safety) | - |

## Estimated Cost

The cost of belzutifan is not yet known.

## Relevant Guidance

### NICE Guidance

- 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

### 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.[21]
- European Society for Medical Oncology (ESMO). Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2019.[22]
- West Midlands Expert Advisory Group for Urological Cancer. Guidelines for the Management of Renal Cancer. 2016.[23]

## Additional Information

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