Health Technology Briefing
November 2021

Retifanlimab for advanced/metastatic merkel cell carcinoma

Company/Developer	Incyte Corporation

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 26650	NICE ID: 10324	UKPS ID: Not Available

Licensing and Market Availability Plans

Currently in phase II clinical trials

Summary

Merkel cell carcinoma (MCC) is a rare type of skin cancer that starts in neuroendocrine cells. Those frequently exposed to ultraviolet light and those with weakened immune systems are most at risk of developing MCC. Symptoms include lumps on the skin, usually found where the skin is most exposed to direct sun. MCC is an aggressive cancer and can rapidly spread within weeks or months meaning early diagnosis and treatment are vital. Prognosis is poor; MCC has a high mortality rate. There are very few treatments licensed for MCC, particularly advanced/metastatic MCC which highlights the need for new treatments to improve prognosis.

Retifanlimab is in development for the treatment of metastatic MCC. It is a type antibody that inhibits a specific protein called programmed cell death 1 (PD-1) from preventing the body producing an immune response. This allows the immune system to target tumour cells, ultimately leading to cell death. Retifanlimab is given as an intravenous (IV) injection and if licensed, would provide an additional treatment for adult patients with advanced/metastatic MCC.

Proposed Indication

Treatment of adult patients with advanced/metastatic MCC.[1]

Technology

Description

Retifanlimab (INCMGA-00012) is a proprietary humanised monoclonal antibody directed against the negative immunoregulatory human cell surface receptor programmed cell death 1 (PD-1), with potential immune checkpoint inhibitory and antineoplastic activities. Upon administration, retifanlimab binds to and inhibits PD-1 and its downstream signalling pathways. This may restore immune function through the activation of T cells and cell-mediated immune responses against tumour cells. PD-1, a transmembrane protein in the immunoglobulin superfamily (IgSF) expressed on T cells, functions as an immune checkpoint that negatively regulates T-cell activation and effector function when activated by its ligands programmed cell death ligand 1 (PD-L1) or 2 (PD-L2); it plays an important role in tumour evasion from host immunity.[2]

In a phase II clinical trial (POD1UM-201, NCT03599713), retifanlimab will be given in 500mg doses every 28 days through IV infusion.[1,3]

Key Innovation

There is currently only one National Institute for Healthcare Excellence (NICE) recommended treatment option for metastatic MCC without prior treatment (avelumab), therefore, this additional treatment would meet a significant unmet need. When MCC spreads to other parts of the body, patients are currently offered chemotherapy - if they are able to tolerate it. The initial response rates are relatively high, but the disease often relapses quite quickly, hence the need for additional treatments.[4]

Similar, to avelumab, retifanlimab is a novel humanised monoclonal antibody directed again PD-1 for this population.[2] In a phase II trial, retifanlimab showed an overall response rate of 46.2% which is higher than that of avelumab studied in a different trial.[5] There has not been a trial comparing the two treatments.

If licensed, retifanlimab will offer an additional treatment for adult patients with advanced/metastatic MCC.

Regulatory & Development Status

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

Retifanlimab is currently in phase II/III trials for a number of indications including squamous cell anal carcinoma, non-small cell lung cancer and endometrial cancer.[6]

Patient Group

Disease Area and Clinical Need

MCC is a rare type of skin cancer. It starts in the merkel cells, which are usually in the top layer of the skin (the epidermis). MCC usually appears as lumps on the skin. The lumps are often bluish red in colour and less than 2 cm across, although they are sometimes larger. MCCs are often found on the head, neck, arms, and legs as these are the areas that get the most direct sun. MCC develops rapidly over weeks or months and can spread to other parts of the body including lymph nodes and bones.[7] MCC pathogenesis is associated with either the presence of Merkel cell polyomavirus or chronic exposure to ultraviolet light (UV), which can cause a characteristic pattern of multiple DNA mutations. MCC is more common in men

than in women and in those over 50. People who have paler skin and those with a weakened immune system are also at increased risk of MCC.[8]

Due to its rarity, there is very little known about the clinical burden of disease of MCC, particularly in the UK. However, globally, increases in incidence have been observed recently but incidence varies greatly between countries.[9] Using National Cancer Registration and Analysis Service (NCRAS) data between 1999 and 2008, there were just 1,515 cases in total; this equates to an increasing incidence rate from 0.1 per 100,000 to 0.2 per 100,000 in this study.[10] Using mid-2020 population estimates, it could be derived that around 113 people every year in England develop MCC.[11] Using data from the same study, 79% of patients with MCC died within 2 years of diagnosis.[10] A study performed in the East of England demonstrated an age-standardised incidence rate of 0.21 per 100,000.[12] The American Cancer Society calculates that the 5-year survival rate for distant MCC is around 19%, using US figures.[13]

Recommended Treatment Options
NICE recommends avelumab as an option for treating metastatic MCC in adults who have not had chemotherapy for metastatic disease.[14] For metastatic MCC, chemotherapy and immunotherapy are the two main treatment options.[7]

Clinical Trial Information

Trial	**POD1UM-201**; NCT03599713; 2018-001627-39; A Phase 2 Study of INCMGA00012 in Participants With Metastatic Merkel Cell Carcinoma **Phase II** – active, not recruiting **Location(s):** US, Canada, EU, UK and Australia **Primary Completion Date**: June 2021
Trial Design	Single group assignment, open label
Population	N=106; 18 years and older; diagnosis of MCC with distant metastatic disease or recurrent, advanced locoregional disease not amenable to surgery or radiation
Intervention(s)	500mg retifanlimab by IV infusion once every 28 days.[3]
Comparator(s)	No comparator
Outcome(s)	Overall Response Rate (ORR) [Time frame: Baseline up to approximately 8 months]. Defined as the percentage of participants with an objective response (complete response [CR] or partial response [PR]) according to Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST v1.1) as determined by independent central radiographic review (ICR). See trial record for full list of other outcomes
Results (efficacy)	• Of the 22 chemo-naïve patients enrolled, 18 have had ≥1 on-study tumour assessment or discontinued. • There are 10 (56%) responders (investigator assessed) with 2 (11%) complete responses and 8 (44%) partial responses. Of these, 6 are confirmed and 4 are unconfirmed ongoing responses. Three patients (17%) have stable disease.[3]

Results (safety)	• As of January 8, 2020, among all treated pts (n=27), 16 (59%) had a treatment-emergent adverse event (TEAE); 6 (22%) were ≥Grade 3, 11 (41%) had a treatment-related TEAE (TRAE), 3 (11%) of which were ≥Grade 3. • The most common TRAEs were asthenia and pruritus (n=3 each). Seven (26%) had a TEAE of special interest (the only immune-related AE occurring in >1 pt was hypothyroidism [n=2]). Two pts (7%) discontinued treatment due to TEAEs (radiculopathy and polyarthritis). • No fatal TEAEs have been reported.[3]

Estimated Cost

The cost of retifanlimab is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Avelumab for untreated metastatic Merkel cell carcinoma (TA691). April 2021.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 Standard Contract for Cancer: Skin (Adult). A12/s/b

Other Guidance

- National Institute for Health and Care Excellence. NICE Pathway. Skin Cancer overview. 2021.[14]
- National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Merkel Cell Carcinoma. 2021.[15]
- European Dermatology Forum (EDF), the European Association of Dermato-Oncology (EADO) and the European Organization for Research and Treatment of Cancer (EORTC). Diagnosis and treatment of Merkel Cell Carcinoma. European consensus-based interdisciplinary guideline. 2015.[16]

Additional Information

Incyte Corporation 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.

References

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