NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
April 2023

Lutetium oxodotreotide with octreotide for treating previously untreated advanced gastroenteropancreatic neuroendocrine tumour

Company/Developer	Advanced Accelerator Applications SA

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 27405	NICE ID: 11875	UKPS ID: N/A

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Lutetium oxodotreotide with octreotide is currently in clinical development for the treatment of patients with metastatic or advanced grade 2 or 3 gastroenteropancreatic neuroendocrine tumour (GEP-NET). A neuroendocrine tumour (NET) is a rare tumour that can develop in many different organs of the body. It affects the cells that release hormones into the bloodstream called neuroendocrine cells. GEP-NET is a rare type of tumour that can grow in various areas of the gut, such as the stomach, small intestine, rectum, colon, appendix, or pancreas. Metastatic or advanced cancer is cancer that had spread around the body from the area it started. GEP-NETs are difficult to diagnose and treat. In addition, there are limited treatment options available for patients with advanced GEP-NET, beyond standard therapy with somatostatin analogues.

Lutetium oxodotreotide is a radiopharmaceutical drug. It attaches to the cancer cells and releases its radioactivity to kill the tumour cell it is bound to via a protein that is very common on the cancer cells but not on the normal body cells. Lutetium oxodotreotide is administered via intravenous infusion (into the patients' veins), every four weeks. If licenced, lutetium oxodotreotide with octreotide will provide an expanded treatment option for patients with grade 2 and grade 3 advanced GEP-NET.

Proposed Indication

Treatment of patients with grade 2 and grade 3 previously untreated advanced gastroenteropancreatic neuroendocrine tumour (GEP-NET), aged 15 years and older.[1]

Technology

Description

Lutetium oxodotreotide (Lutathera) belongs to the pharmacotherapeutic group of therapeutic radiopharmaceuticals. It has a high affinity for somatostatin receptors (SSTR) subtype 2, thus binds to malignant cells, which overexpress SSTR2 receptors.[2] Lutetium oxodotreotide works by attaching to somatostatin receptors, which are found in high numbers in some GEP-NETs. The radioactivity it emits then kills the tumour cells it is attached to but has little effect on neighbouring cells.[3]

Lutetium oxodotreotide in combination with octreotide is currently in clinical development for the treatment of patients with grade 2 or 3 GEP-NET. In the phase III clinical trial NETTER 2 (NCT03972488), patients are given 4 intravenous (IV) administrations of 7.4 gigabecquerels (GBq) lutetium (every 8+/-1 weeks) in combination with a long-acting octreotide (30mg every 8 weeks during lutetium treatment and 4 weeks after last lutetium treatment).[1]

Key Innovation

Lutetium oxodotreotide is the first radiopharmaceutical for PRRT approved for the treatment of SSTR positive GEP-NETs.[4] The therapeutic tracer combines a suitable radionuclide with a peptide that specifically binds to a peptide receptor, which is upregulated to a high concentration on tumour cells and at low physiological levels on normal tissues, to deliver the cytotoxic radiation.[4] In a phase III trials, at 20months, 65% of patients in the Lutathera plus octreotide LAR (30mg) group were living progression free and had a significant higher response rate than the high-dose octreotide LAR group.[5]

If licenced, lutetium oxodotreotide in combination with octreotide will give an additional treatment option for patients with grade 2 and grade 3 advanced GEP-NETs.

Regulatory & Development Status

Lutetium oxodotreotide has Marketing Authorization in the EU/UK for use in treating grade 1 and 2 GEP-NETs.[3,6]

Lutetium oxodotreotide is currently in phase II/III clinical development for the following indications:[7]

- Meningioma
- Pheochromocytoma
- Carcinoid syndrome
- Metastatic Prostate Carcinoma
- Metastatic Breast Cancer
- Metastatic Nasopharyngeal Cancer
- Neuroblastoma
- Merkel Cell Carcinoma
- Lung tumours
- Glioma

Lutetium oxodotreotide was granted an orphan medicine designation for the treatment of GEP-NETs by the European medicine agency (EMA) on the 31st January 2008.[3,8]

Patient Group

Disease Area and Clinical Need

NETs are rare tumours that develop cells of the neuroendocrine systems.[9] It affects the cells that release hormones into the bloodstream called neuroendocrine cells.[10] Neuroendocrine cells are similar to nerve cells, and they make chemical messengers called hormones. GEP-NETs can grow in various areas of the gut, such as the stomach, small intestine, rectum, colon, appendix, or pancreas. GEP-NETs are usually slow growing. It is not known what causes NETs. NETs generally can be graded as 1, 2 or 3 depending on how quickly the cells divide to make new ones (mitotic count), amount of ki-67 protein in percentage and the number of dead cells present.[11] GEP-NETs grade 2 cells look less like normal cells and are more likely to grow and spread while grade 3 cells look very abnormal, tend to grow quickly and are more likely to spread.[12] GEP-NETs grades can give an estimate of how the disease affects patients and responds to treatments. NETs can affect people of any age, including children, but the average age to be diagnosed is around 50 to 60 years old. Around 1 in 20 (5%) of NETs occur in people with a genetic condition called multiple endocrine neoplasia 1, also people with other genetic conditions such as tubular sclerosis and Von Hippel-Lindau syndrome also carry a higher risk of developing NETs.[10,13] The symptoms of NETs depend on the organs affected and the hormones it produced, these can include diarrhoea, constipation, abdominal pains, wheezing or persistent cough, cramps flushing hypoglycaemia. Some tumours present asymptomatically.[13,14]

Each year in the UK, around 6,000 people are diagnosed with NETs with a prevalence of 35 cases per 100,000 cases.[15,16] Between 1995 and 2018, in England, the incidence of neuroendocrine cancers rose by 371%.[17] The overall 5-year survival rate in GEP-NET has been reported as approximately 70%, spanning from 38% for pancreatic NETs to 89% for rectal NETs, and approaching 100% for gastric NETs (type I).[18]

Recommended Treatment Options

Everolimus and sunitinib are recommended by NICE as options for treating well- or moderately differentiated unresectable or metastatic (NETs) of pancreatic origin in adults with progressive disease.[19] There are no specific documented current treatment options for grade 2 and grade 3 advanced GEP-NETs.

Clinical Trial Information

Trial	**NETTER-2;** NCT03972488, 2019-001562-15; A Phase III Multi-center, Randomized, Open-label Study to Evaluate the Efficacy and Safety of Lutathera in Patients With Grade 2 and Grade 3 Advanced GEP-NET **Phase III** - Active, not recruiting **Location(s):** 5 EU countries, UK, USA, Canada, and other countries **Primary completion date**: November 2023
Trial Design	Randomised, parallel assignment, open label
Population	N= 222; patients aged 15 years above with metastasised or locally advanced, well differentiated, Grade 2 or Grade 3 GEP-NET.
Intervention(s)	Lutetium oxodotreotide (7.4 GBq/200 mCi x 4 administrations every 8 +/- 1 weeks) and long-acting octreotide (30 mg every 8 weeks during lutetium oxodotreotide treatment and every 4 weeks after last lutetium oxodotreotide treatment)

Comparator(s)	High dose long-acting octreotide (60 mg every 4 weeks)
Outcome(s)	Primary outcomes: • Progression Free Survival (PFS) [Time frame: through Week 72 until 99 PFS events are reached] • Time from randomization to the first line progression (centrally assessed according to RECIST 1.1 or death due to any cause) See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

One cycle of four administrations of 7.4GBq Lutetium oxodotreotide at list price costs £71,500.00.[20]

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Lutetium (177Lu) oxodotreotide for treating unresectable or metastatic neuroendocrine tumours (TA539). August 2018.
- NICE technology appraisal. Everolimus and sunitinib for treating unresectable or metastatic neuroendocrine tumours in people with progressive disease (TA449). June 2017.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Specialised Endocrinology Services (Adult). A03/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). Gastroenteropancreatic neuroendocrine neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. 2020.[21]
- European Neuroendocrine Tumour Society (ENETS). Consensus Guidelines for High-Grade Gastroenteropancreatic Neuroendocrine Tumours and Neuroendocrine Carcinomas. 2016.[22]
- ENETS. Consensus Guidelines Update for Gastroduodenal Neuroendocrine Neoplasms. 2016.[23]
- ENETS. Consensus Guidelines for the Management of Patients with Digestive Neuroendocrine Tumours: An Update. 2016.[24]

Additional Information

Advanced Accelerator Applications SA 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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