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HEALTH TECHNOLOGY BRIEFING FEBRUARY 2020

Eryaspase in addition to chemotherapy for treating advanced or metastatic pancreatic cancer – second-line

NIHRIO ID	9912	**NICE ID**	10204
Developer/Company	Erytech Pharma	**UKPS ID**	N/A

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

SUMMARY

Eryaspase in addition to chemotherapy is in clinical development for the treatment of patients with advanced or metastatic pancreatic ductal adenocarcinoma (PDAC) whose disease has progressed following one prior treatment line of anti-cancer therapy. PDAC develops from ducts in the pancreas that carry digestive juices from the pancreas to the intestines. Pancreatic cancer is considered metastatic when the cancer has spread from the pancreas to other parts of the body, most often the liver, abdominal wall, lungs, bones or faraway lymph nodes. Symptoms of advanced or metastatic pancreatic cancer are often non-specific such as abdominal or back pain, weight loss, loss of appetite, yellowing of the skin, eyes or both, or nausea. A small proportion of PDAC cases have a genetic basis but the majority are caused by modifiable risk factors such as smoking, alcohol and obesity.

Eryaspase is administered intravenously and works by reducing the amount of an essential protein called asparagine which is available to tumour cells, resulting in the death of these cells. If licensed, eryaspase in addition to chemotherapy will offer an additional treatment option for patients with metastatic PDAC who have failed previous chemotherapy.

PROPOSED INDICATION

Treatment of adults with advanced or metastatic pancreatic ductal adenocarcinoma (PDAC) – second-line.[1]

TECHNOLOGY

DESCRIPTION

Eryaspase (Graspa, ERY001) is manufactured from commercially available L-asparaginase, derived from E.coli, encapsulated within donor derived red blood cells (RBC) that are qualified for transfusion applications.[2,3] The RBCs in eryaspase transport asparagine from plasma through sodium coupled neutral amino acid transporters (SNAT 3/5) into the RBC interior. The enzymatic activity of the entrapped L-asparaginase cleaves the entrapped L-asparagine into aspartic acid and ammonium, resulting in asparagine decrease in the plasma.[2] Asparagine is a critical amino acid for the growth and survival of cancer cells.[3] Depletion of plasma asparagine inhibits protein synthesis, thereby inhibiting nucleotide synthesis and results in apoptotic cell death of tumour cells.[4] A high proportion (79%) of resected pancreatic adenocarcinomas have low or null asparagine synthetase.[2,5] Therefore, these tumour cells require an exogenous supply of asparagine that can only be obtained by diffusion from the environment outside the cell.[2]

Eryaspase in addition to chemotherapy is in clinical development for the second-line treatment of adults with advanced or metastatic PDAC who have failed one previous line of chemotherapy. In the phase III clinical trial (NCT03665441, Trybeca-1) patients receive 100 U/kg of eryaspase every two weeks in addition to chemotherapy or chemotherapy alone.[1]

INNOVATION AND/OR ADVANTAGES

Metastatic adenocarcinoma of the pancreas that has progressed after first-line treatment is associated with a poor prognosis because there are few treatments available and current treatments are limited in efficacy. Therefore, there is a need for additional second-line treatment options.[6]

Asparaginase products result in systemic degradation of asparagine but are also known to have a glutaminase effect. The degradation of glutamine has been demonstrated to be associated with clinical toxicity. The encapsulated form of asparaginase (eryaspase) displayed significantly decreased glutaminase activity compared to the non-encapsulated form. The encapsulated eryaspase has a 3.5 fold increase in selectivity for asparagine over glutamine. This may explain the observed decrease in the frequency of adverse events in clinical trials with eryaspase compared to non-encapsulated native asparaginase.[3]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

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

Eryaspase was given an orphan drug designation for the treatment of pancreatic cancer by the EMA in May 2009.[7]

Eryaspase is currently in phase II/III development for the treatment of triple negative breast cancer and acute lymphoblastic leukaemia.[8]

PATIENT GROUP

DISEASE BACKGROUND

Pancreatic cancer is caused by the abnormal and uncontrolled growth of cells in the pancreas, a large gland that is part of the digestive system.[9] The most common type of pancreatic cancer (accounting for 95% of cases) is pancreatic ductal adenocarcinoma (PDAC) which develops from ducts (exocrine glands) in the pancreas that carry digestive juices containing enzymes into the main pancreatic duct and then on into the duodenum – the first part of the small intestine which is involved in the chemical digestion of food. PDAC can grow anywhere in the pancreas, though it is most often found in the head of the pancreas.[10] Metastatic cancer refers to a cancer where the disease has spread from where it first started to another area of the body. Pancreatic cancer often spreads to the liver, abdominal wall, lungs bones or faraway lymph nodes.[11]

The majority of PDAC cases are sporadic with no known genetic predisposition. Tobacco smoking, alcohol and obesity are known modifiable risk factors. Studies have suggested that approximately 36% of pancreatic cancers in men and 39% in women are linked to lifestyle factors. New onset diabetes in subjects older than 50 years has also been documented as a high risk factor in sporadic PDAC.[12] Both genetic and modifiable risk factors contribute to the development of PDAC. A hereditary component has been identified in approximately 10% of PDAC cases with a specific germline mutation being implicated in 20% of those cases.[13]
Symptoms of pancreatic cancer include: abdomen or back pain, weight loss, jaundice (yellowing of the skin, eyes or both) with or without itching, loss of appetite, nausea, change in stool, pancreatitis and recent-onset diabetes.[11]

CLINICAL NEED AND BURDEN OF DISEASE

Pancreatic cancer was the 11th most common cancer in the UK, accounting for 3% of all new cancer cases in 2016. Incidence rates for pancreatic cancer in the UK were highest in people aged 85 to 89 years, between 2014 and 2016. Incidence rates for pancreatic cancer cases are projected to rise by 6% in the UK between 2014 and 2035, to 21 cases per 100,000 people by 2035.[14]

In England, in 2017, there were 8,829 registrations of newly diagnosed cases of malignant neoplasm of pancreas (ICD-10 code C25) and the age-standardised rate per 100,000 population was 19.4 among males and 15.2 among females.[15] In England, in 2018-19, there were 41,308 finished consultant episodes (FCEs) for malignant neoplasm of the pancreas (ICD-10 code C25) and 32,610 admissions resulting in 93,999 FCE bed days and 24,103 day cases.[16]

In England, in 2017, there were 8,305 deaths with malignant neoplasm of pancreas (ICD-10 code C25) recorded as the underlying cause.[17] The age-standardised 1-year and 5-year survival for persons diagnosed pancreatic cancer in England in 2017 was 25.4% and 7.3% respectively.[18]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Signs and symptoms of pancreatic cancer can often be vague and non-specific so many patients are not diagnosed until their cancer is at an advanced stage. At this stage, surgery - the only treatment that has the potential to cure the disease - is usually not possible.[19] Consequently, patients with advanced or metastatic disease may be offered chemotherapy, radiotherapy or palliative surgery to help control tumour growth and symptoms. These may be given alone or in combination with each other.[20]

CURRENT TREATMENT OPTIONS

For locally advanced pancreatic cancer, NICE guidelines recommend giving combination chemotherapy if they are well enough to tolerate it and gemcitabine monotherapy is considered for patients not well enough to tolerate combination therapy.[21]

NICE have recommended the following treatment options for patients with metastatic PDAC who have failed first-line therapy:[22]

- Pegylated liposomal irinotecan for treating pancreatic cancer after gemcitabine

Additionally physicians may consider the following treatment options for patients with metastatic PDAC who have failed first-line therapy. Although their use is common in UK clinical practice they do not have a UK Marketing Authorisation for this indication:[22,21]

- Oxaliplatin based chemotherapy as a second-line treatment for people who have not had first-line oxaliplatin
- Gemcitabine based chemotherapy as second-line treatment for people whose cancer has progressed after first line FOLFIRNOX

PLACE OF TECHNOLOGY

If licensed, eryaspase will offer a new treatment option for patients with advanced or metastatic PDAC who have failed one prior line of cancer chemotherapy.

CLINICAL TRIAL INFORMATION

Trial	**Trybeca-1,** NCT03665441, Eudra CT 2018-000572-15, GRASPANC-2018-01; Study of Eryaspase in Combination With Chemotherapy Versus Chemotherapy Alone as Second Line treatment in PDAC **Phase III** **Locations:** 11 EU countries (incl UK) and USA
Trial design	Randomized, parallel assignment, open label
Population	N= 500 (planned); adults aged 18 years and older; stage III or IV histologically confirmed pancreatic ductal adenocarcinoma; have received only one prior line of systemic chemotherapy; radiological evidence of disease progression following most recent prior treatment
Intervention(s)	100 U/kg eryaspase + standard of care chemotherapy (IV)

Comparator(s)	Standard of care chemotherapy alone
Outcome(s)	Overall Survival [Time frame: 1 year after last patient randomized]
Results (efficacy)	-
Results (safety)	-

Trial	NCT02195180, Eudra CT 2013-004262-34, GRASPANC 2013-03; Efficacy and Safety of L-asparaginase Encapsulated in RBC Combined With Gemcitabine or FOLFOX in 2nd Line for Progressive Metastatic Pancreatic Carcinoma **Phase II** **Location:** France
Trial design	Randomized, parallel assignment, open-label
Population	N=141 participants; adults aged 18 years and older; histologically confirmed advanced or metastatic exocrine pancreatic adenocarcinoma; only 1 prior systemic therapy for advanced or metastatic disease
Intervention(s)	Eryaspase in addition to standard of care chemotherapy (IV)
Comparator(s)	Standard of care chemotherapy alone
Outcome(s)	• Overall survival [Time frame: from last study treatment assessment visit until patient's death, loss to follow up or study closure] • Progression free survival [Time frame: from date of randomization to first documented progression of disease, death of any cause or until start of new anti-cancer treatment, whichever came first, assessed up to 24 months]
Results (efficacy)	Patients with no or low asparagine synthetase demonstrated a hazard ratio (HR) of 0.73 for progression free survival (PFS) and 0.62 for overall survival (OS) therefore the trial met its primary endpoint. Median OS and PFS in patients with low asparagine synthetase expression were 6.2 months in the eryaspase arm versus 4.9 months in the control arm and 2.0 months in the eryaspase arm versus 1.8 months in the control arm respectively. In the entire patient population eryaspase led to improvement of OS (median 26.1 weeks) compared to control (median 19 weeks); HR of 0.57 (P=0.03). Similarly, eryaspase led to significant improvement in PFS.[23, 24]
Results (safety)	Overall treatment was well tolerated, with asthenia, myelosuppression, nausea and vomiting being the most frequent events in both arms. The most frequent grade ¾ adverse events in the eryaspase arm were gamma-glutamyltransferase increase (17.2%), neutropenia (12.9%) and physical health deterioration (12.9%).[23, 24]

ESTIMATED COST

The estimated cost of eryaspase is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. PEGPH20 with nab-paclitaxel and gemcitabine for treating metastatic pancreatic cancer (TA10402). Expected publication date to be confirmed.
- NICE technology appraisal. Pegylated liposomal irinotecan for treating pancreatic cancer after gemcitabine (TA440). April 2017.
- NICE clinical guideline. Pancreatic cancer in adults: diagnosis and management (NG85). February 2018.
- NICE quality standard. Pancreatic cancer (QS177). December 2018.
- NICE diagnostics guidance. Fluorouracil chemotherapy: The My5-FU assay for guiding dose adjustment (DG16). December 2014.

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.
- NHS England. 2013/14 NHS Standard Contract for Hepatobiliary and Pancreas (Adult). A02/S/a.

OTHER GUIDANCE

- Journal of the National Comprehensive Cancer Network. Pancreatic Adenocarcinoma Version 2.2017, NCCN Clinical Practice Guidelines in Oncology. 2017.[25]
- European Society for Medical Oncology. Cancer of the Pancreas: ESMO Clinical Practice Guidelines. 2015.[26]

ADDITIONAL INFORMATION

Erytech Pharma 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.

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