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siG12D-LODER in addition to standard chemotherapy for locally advanced pancreatic cancer

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LAY SUMMARY

Pancreatic cancer is caused by the abnormal and uncontrolled growth of cells in the pancreas – a large gland that is a part of the digestive system. Locally advanced pancreatic cancer (LAPC) means the cancer has spread into nearby large blood vessels and possibly the lymph nodes. It may have spread into the stomach, bile duct or small bowel, but not to organs further away in the body. More than three quarters of patients with pancreatic cancer have locally advanced or metastatic disease at the time of diagnosis, and are not candidates for surgical curative intervention. The cause of pancreatic cancer is not fully understood but several risk factors have been identified, one of which is a mutation in KRAS genes.

siG12D-LODER is a gene therapy currently being developed for the treatment of LAPC. It is a small biodegradable material containing the active component of the drug (siG12D) and is injected directly into the tumour. siG12D-LODER acts by inhibiting the KRAS genes and therefore reducing tumour growth in the pancreas. If licensed, siG12D-LODER in addition to standard chemotherapy will offer an additional treatment option for patients with locally advanced pancreatic cancer.

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TARGET GROUP

Pancreatic cancer (American Joint Committee (AJCC) stage III, unresectable, locally advanced) – first line; in combination with chemotherapy

TECHNOLOGY

DESCRIPTION

siG12D-LODER (Antisense KRAS RNA gene therapy) is a miniature biodegradable polymeric matrix containing the drug siG12D that is injected into the tumour using a standard biopsy procedure. LODER (Local Drug EluteR) is the specialized bio-polymeric scaffold that contains the siG12D which is an anti-KRAS (G12D) small interference Ribonucleic Acid (siRNA). siG12D-LODER has shown to efficiently protect the encapsulated siRNA against enzymatic degradation, while releasing the drug within a tumour in vivo in mice.[1] Mutated KRAS is a documented driver for malignant transformation, occurring early during the pathogenesis of cancers such as lung and pancreatic adenocarcinomas,[2] with most of them occurring at codon 12 of the oncogene G12D.[3] Small interfering RNA (siRNA) is able to silence target genes with high efficiency and specificity.[4] Therefore, suppression of KRAS expression by RNAi leads to growth inhibition of pancreatic cancer cells.

In the phase II trial (PROTACT; NCT01676259) of siG12D LODER in combination with chemotherapy in patients with locally advanced pancreatic cancer, siG12D-LODER was implanted in the subject's tumour using a EUS (Endoscopic Ultrasound) guided biopsy needle and a dose of 2.8 mg (eight 0.35 mg siG12D-LODERs) administered in 12-week cycles.[5]

siG12D-LODER does not have Marketing Authorisation in the EU or the UK for any indication.

INNOVATION and/or ADVANTAGES

siG12D-LODER delivers the drug after being implanted within the tumour and the active agent siG12D was found to be non-toxic in all doses in vivo.[1] If licensed, it will offer an additional treatment option in combination with chemotherapy for locally advanced pancreatic cancer.

DEVELOPER

Silenseed Ltd

AVAILABILITY, LAUNCH or MARKETING

siG12D-LODER was designated as an orphan drug in the USA for pancreatic ductal adenocarcinoma in January 2015.[6]

PATIENT GROUP

BACKGROUND

Pancreatic cancer is caused by the abnormal and uncontrolled growth of cells in the pancreas – a large gland that is a part of the digestive system.[7] Pancreatic ductal adenocarcinoma (PDAC) is the most common pancreatic neoplasm, responsible for 90% of pancreatic cancer cases.[8]

Locally advanced pancreatic cancer (LAPC) means the cancer has spread into nearby large blood vessels and possibly the lymph nodes. It may have spread into the stomach, bile duct or duodenum (small bowel), but not to organs further away in the body.[9] Mutation in the KRAS genes is one of the causes of tumour growth in the pancreas.[2]

In the early stages, a tumour in the pancreas does not usually cause any symptoms, which can make it difficult to diagnose. The first noticeable symptoms of pancreatic cancer are often pain in the back or stomach area, unexpected weight loss and jaundice. Other possible symptoms of pancreatic cancer include nausea and vomiting, bowel changes, fever and shivering, indigestion and blood clots.[7]

The cause of pancreatic cancer is not fully understood but a number of risk factors for developing the condition have been identified which include age, smoking and having a history of certain health conditions such as diabetes, chronic pancreatitis (long-term inflammation of the pancreas), stomach ulcer and Helicobacter pylori infection (a stomach infection).[7]

Unlike potentially curable (resectable) pancreatic cancer, where preoperative treatments can potentially improve resectability, patients with LAPC rarely undergo resection with curative intent. Local control and quality of life (QOL) are the important issues in LAPC. Local symptoms are often difficult to manage and contribute to poor QOL.[10]

CLINICAL NEED and BURDEN OF DISEASE

Around half of all new cases of pancreatic cancer are diagnosed in people aged 75 years or over. Pancreatic cancer is uncommon in people under 40 years of age.[7] About 80% to 85% of patients with pancreatic cancer have advanced disease at the time of diagnosis, i.e. stage III (LAPC) or stage IV (metastatic), and are not candidates for surgical curative intervention.[1]

In England in 2016, there were 8,455 registrations of newly diagnosed cases of malignant neoplasm of pancreas (ICD-10 code C25).[11] Considering 80-85% of patients have locally advanced or metastatic cancer at the time of diagnosis, the number patients in 2016 out of 8,455 cases of pancreatic cancer with LAPC or metastatic cancer would be between 6,764 and 7,187.

Across the UK, the incidence rate is expected to increase from 19.5 per 100,000 European age-standardised rate (EASR) (9,616 cases) in 2014 to 20.65 per 100,000 EASR (15,157 cases) in 2035.[12] In England and Wales in 2016, there were 8,315 deaths where malignant neoplasm of pancreas (ICD-10 code C25) was recorded as the underlying cause.[13]

Latest published survival statistics (2016, patients diagnosed in 2011-2015) report stated 1-year survival rate of 23.7% and 5-year survival rate of 6.9% (age-standardised) for patients with pancreatic cancer.[14]

According to the Hospital Episode Statistics (HES) data, in 2016-17 there were 28,204 admissions due to neoplasm of the pancreas which resulted in 91,409 FCE bed days (ICD-10 code C25).[15]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Pancreatic cancer (locally advanced, metastatic) - masitinib (GID-TAG330). Expected publication date: TBC.
- NICE technology appraisal in development. Paclitaxel as albumin-bound nanoparticles with gemcitabine for adjuvant treatment of pancreatic cancer (GID-TA10329). Expected publication date: TBC.
- NICE technology appraisal in development. Pancreatic cancer - capecitabine (GID-TAG394). Expected publication date: TBC.
- NICE quality standard in development. Pancreatic cancer (GID-QS10061). Expected publication date: 20 December 2018.
- NICE interventional procedure guidance. Irreversible electroporation for treating pancreatic cancer (IPG579). May 2017.
- NICE guidelines. Pancreatic cancer in adults: diagnosis and management (NG85). February 2018.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Pancreatic (Adult). A02/S/b.

OTHER GUIDANCE

- Locally Advanced, Unresectable Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline. 2016.[10]
- Pancreatic Adenocarcinoma. NCCN Clinical Practice Guidelines in Oncology. 2016.[16]
- Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2015.[17]

CURRENT TREATMENT OPTIONS

Pancreatic cancer usually causes few symptoms until the disease has reached an advanced stage, so most cases are diagnosed when curative treatment is not possible. Because potentially curative surgery is rarely an option, most patients can only be offered palliative treatment to relieve their symptoms. Stenting of the bile duct and duodenum can be used to relieve obstruction caused by pancreatic cancer, and sometimes surgical bypass is needed. Other treatment options include palliative chemotherapy and radiotherapy.[18]

Current chemotherapy treatment options include:[19]

- FOLIFIRINOX
- gemcitabine with capecitabine
- gemcitabine with nab paclitaxel
- gemcitabine on its own

According to recently published NICE guidelines (NG85), systemic combination chemotherapy may be offered to patients with LAPC who are well enough to tolerate it. Gemcitabine can be considered for people with LAPC who are not well enough to tolerate combination chemotherapy. When using chemoradiotherapy, capecitabine may be considered as the radiosensitiser.[20]

EFFICACY and SAFETY

Trial	PROTACT, NCT01676259, SLSG12D-P2; locally advanced pancreatic cancer, siG12D-LODER, in combination with chemotherapy, phase II
Sponsor	Silenseed Ltd
Status	Ongoing
Source of Information	Trial registry[5]
Location	United States
Design	Randomised, parallel assignment, open label
Participants	n=80 (planned); aged 18 years and older; pancreatic cancer; locally advanced, unresectable
Schedule	2.8 mg (eight 0.35 mg siG12D-LODERs) will be administered in 12-week cycles in combination with chemotherapy (Gemcitabine+nab-Paclitaxel)
Follow-up	Not reported
Primary Outcomes	Progression-free survival (PFS) in the study population [Time Frame: One year]
Secondary Outcomes	Not reported
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Primary completion date reported as Nov 2019

ESTIMATED COST and IMPACT

COST

The cost of siG12D-LODER is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ Other:

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☒ Increased use of existing services

☐ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other:

☐ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☒ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs:

☐ Other reduction in costs:

☐ Other:

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified:

☒ None identified

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