

Health Technology Briefing May 2024

Irinotecan liposome injection with oxaliplatin, 5-fluorouracil and leucovorin for previously untreated metastatic pancreatic cancer

Company/Developer

Servier Laboratories Ltd

New Active Substance

Significant Licence Extension (SLE)

NIHRIO ID: 28399

NICE ID: N/A

UKPS ID: 671073

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Irinotecan liposome injection with oxaliplatin, 5-fluorouracil and leucovorin is in development for the treatment of metastatic pancreatic cancer. Pancreatic cancer occurs when abnormal cells in the pancreas divide and grow in an uncontrolled way, forming a growth (tumour). Cells from the tumour can spread to other parts of the body (metastases). Metastatic pancreatic cancer has a poor prognosis, due to late diagnosis, and it cannot be cured. Treatment for metastatic pancreatic cancer aims to control the symptoms and increase survival time.

The active substance in onivyde pegylated liposomal, irinotecan, is a cancer medicine that belongs to the group of medicines called topoisomerase inhibitors. It blocks an enzyme called topoisomerase I, which is involved in copying cell DNA needed to make new cells. By blocking the enzyme, cancer cells are prevented from multiplying and they eventually die. In onivyde pegylated liposomal, irinotecan is enclosed in tiny fat particles called liposomes. The liposomes are expected to accumulate in the tumour and release the medicine slowly over time, thereby decreasing the rate at which irinotecan is removed from the body and allowing it to act for longer. If licensed, this combination could provide a new first-line treatment option to adult patients with metastatic pancreatic cancer.

Proposed Indication

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.

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Adult patients with metastatic adenocarcinoma of the pancreas who have not previously received chemotherapy.¹

Technology

Description

Irinotecan injection (Onivyde, Onivyde pegylated liposomal, Nal-IRI) is a topoisomerase I inhibitor encapsulated within a liposome. Irinotecan blocks an enzyme called topoisomerase I, which is involved in copying cell DNA needed to make new cells. By blocking the enzyme, cancer cells are prevented from multiplying and they eventually die.² The liposomes are expected to accumulate within the tumour and release the medicine slowly over time, thereby allowing it to act for longer.³

Irinotecan liposome injection in combination with oxaliplatin, 5-fluorouracil and leucovorin is in phase III clinical development for first-line treatment of patients with metastatic adenocarcinoma of the pancreas.¹ In the phase III trial (NCT04083235), patients were given irinotecan liposome injection (50mg/m²), oxaliplatin (60mg/m²) and 5-fluorouracil (2400mg/m²) and leucovorin (400mg/m²) injections on day 1 and day 15 of each 28-day cycle.¹

Key Innovation

Metastatic pancreatic cancer has poor prognosis and treatment is aimed at controlling/preventing symptoms rather than curing the disease.⁴ Irinotecan liposome injections may offer longer lasting and more potent anti-cancer effects, as it is able to remain within cancer cells longer due to liposome accumulation within tumour cells. As irinotecan is not expelled from the body as quickly, it releases the medicine more slowly and therefore has a therapeutic benefit over a longer time period.² Treatment with multiple cytotoxic drugs (oxaliplatin and 5-fluorouracil) reduces the risk of cells becoming chemo-resistant, as DNA replication in cancer cells is being targeted through multiple different mechanisms by different drugs.⁵ In the phase I/II trial NCT02551991, the treatment regime of irinotecan liposome injection with oxaliplatin, 5-fluorouracil and leucovorin was generally well-tolerated.⁶

If licensed, the combination of irinotecan liposome injection with oxaliplatin, 5-fluorouracil and leucovorin will offer an additional treatment option to previously untreated patients who have limited, well tolerated therapies available.

Regulatory & Development Status

Treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil (5-FU) and leucovorin (LV), in adult patients who have progressed following gemcitabine based therapy.³

Oxaliplatin in combination with 5-fluorouracil and leucovorin is currently marketed in the UK for the following indications:⁷

- treatment of metastatic colorectal cancer
- stage III (Dukes' C) colon cancer after complete resection of primary tumour

5-fluorouracil in combination with salicylic acid is currently marketed in the UK for the treatment of low or moderately thick hyperkeratotic actinic keratosis.⁸

5-fluorouracil is also currently marketed in the UK as a monotherapy for the following indications:⁹

- solid tumours (including gastro-intestinal tract cancers and breast cancer)
- colorectal cancer
- superficial malignant and pre-malignant skin lesions

Leucovorin in combination with 5-fluorouracil is currently marketed in the UK for the treatment of colorectal cancer.¹⁰

Leucovorin is also currently marketed in the UK as a monotherapy for the following indications:¹⁰

- prevention of methotrexate-induced adverse effects
- suspected methotrexate overdose

The combination of irinotecan liposome injections with oxaliplatin, 5-fluorouracil and leucovorin is not currently in any other phase II/III clinical trials.¹¹

Patient Group

Disease Area and Clinical Need

The pancreas is a gland that produces digestive juices and hormones. Pancreatic cancer occurs when abnormal cells in the pancreas start to divide and grow in an uncontrolled way and form a growth (tumour).¹² The cause of pancreatic cancer is unknown, however ageing, smoking, excessive alcohol consumption, obesity, genetic risk factors and a range of other medical conditions (e.g. diabetes, gallstones, and metabolic syndrome) have all been linked to increased risk.¹³ Metastatic cancer refers to a cancer where the disease has spread from where it first started to another area of the body. Pancreatic cancer cells can acquire pro-metastatic traits early in the disease process, meaning it can spread rapidly to other parts of the body such as the liver, lungs or bones.^{14,15} The main symptoms of pancreatic cancer include jaundice (yellowing of the whites of your eyes and skin, dark urine and paler faeces than normal), weight loss, fatigue, fever, sickness, diarrhoea or constipation, abdominal pain and symptoms of indigestion.¹⁶

Between 2016-2018, there were 10,452 new cases of pancreatic cancer in the UK, and 9,558 deaths from pancreatic cancer between 2017-2019 in the UK.¹⁷ Approximately 80% of patients diagnosed with pancreatic cancer are diagnosed at either stage III or IV, when the cancer has spread to other parts of the body (locally advanced or metastasised).¹⁸ Between 2022-2023, there were 46,385 finished consult episodes (FCE) for malignant neoplasm of the pancreas (ICD10 code: C25), resulting in 30,151 day cases and 88,503 FCE bed days.¹⁹ In England in 2017, there were 8,829 registrations of newly diagnosed malignant neoplasms of the pancreas (ICD10 code: C25), and the age-standardised rate per 100,000 population was 19.4 among males and 15.2 among females.²⁰

Recommended Treatment Options

NICE recommends the following treatments for untreated metastatic pancreatic cancer:

- FOLFIRINOX (combination of folinic acid, fluorouracil, irinotecan and oxaliplatin).²¹
- paclitaxel as albumin-bound nanoparticles with gemcitabine is recommended if other combination chemotherapies are unsuitable and they would otherwise have gemcitabine monotherapy and if the company provides it with the discount agreed in the patient access scheme.²²

Clinical Trial Information

Trial	<p>NCT04083235; EudraCT 2018-003585-14; An open-label, randomised, multicentre, phase III study of irinotecan liposome injection, oxaliplatin, 5-fluorouracil/leucovorin versus nab-paclitaxel plus gemcitabine in subjects who have not previously received chemotherapy for metastatic adenocarcinoma of the pancreas</p> <p>Phase III – Active, not recruiting.</p> <p>Location(s): 10 EU countries, UK, and other countries</p> <p>Primary completion date: July 2022</p>
Trial Design	Randomised, parallel assignment, open label.
Population	N=770 (actual); adults with metastatic adenocarcinoma of the pancreas who have not previously been treated for metastatic disease.
Intervention(s)	Irinotecan liposome injection plus oxaliplatin and 5-fluorouracil/leucovorin delivered via injection on days 1 and 15 of each 28-day cycle.
Comparator(s)	Nab-paclitaxel and gemcitabine delivered via injection on days 1, 8 and 15 of each 28-day cycle.
Outcome(s)	<p>Primary outcome measure: overall survival [Time frame: Up to a maximum of 893 days].</p> <p>See trial record for full list of other outcomes.</p>
Results (efficacy)	See trial record.
Results (safety)	See trial record.

Estimated Cost

Irinotecan (as Irinotecan sucrosfate salt pegylated liposomal) is already marketed in the UK a 43mg/10ml vial costs £615.35.²³

Oxaliplatin is already marketed in the UK, the cost of a 50mg/10ml vial ranges from £146.80-£196.74. The cost of a 100mg/20ml vial from £289.50-£393.98. The cost of a 200mg/40ml vial ranges from £591.26-£787.90.²⁴

5-fluorouracil is already marketed in the UK, the cost of a 1g/20ml vial for injection ranges from £12.16-£12.80. The cost of a 500mg/10ml vial for injection ranges from £6.08-£6.40.²⁵

Leucovorin is already marketed in the UK, The cost of a 50mg/5ml vial ranges from £20.00-£26.02. The cost of a 100mg/10ml vial ranges from £37.50-£48.59. The cost of a 200mg/20ml vial is £92.32. The cost of a 300mg/30ml vial containing of leucovorin is £100.00. The cost of a 350mg/35ml vial is £153.47.²⁶

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Paclitaxel as albumin-bound nanoparticles with gemcitabine for untreated metastatic pancreatic cancer (TA476). September 2017
- NICE clinical guideline. Pancreatic cancer in adults: diagnosis and management (NG85). February 2018.
- NICE quality standard. Pancreatic cancer (QS177). December 2018.

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

Other Guidance

- European Society for Medical Oncology. Conroy. T, Pfeiffer. P, Vilgrain. V, *et al.* Pancreatic cancer: ESMO Clinical Practice Guideline for diagnosis, treatment, and follow-up. 2023.²⁷
- American Society of Clinical Oncology. Sohal. D, Kennedy. E, Cinar. P, *et al.* Metastatic Pancreatic Cancer: ASCO Guideline Update. 2020.²⁸
- Journal of the National Comprehensive Cancer Network. Tempero. MA, Malafa. MP, Al-Hawary. M, Behrman. SW, Benson. AB *et al.* Pancreatic Adenocarcinoma, Version 2.2021. 2021.²⁹

Additional Information

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