NIHR | Innovation Observatory

HEALTH TECHNOLOGY BRIEFING
DECEMBER 2019

Pemigatinib for locally advanced or metastatic, relapsed or refractory cholangiocarcinoma with FGFR2 fusion or rearrangement

NIHRIO ID	13206	**NICE ID**	10295
Developer/Company	Incyte Corp	**UKPS ID**	Not Available

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

SUMMARY

Pemigatinib is in clinical development for adults with locally advanced or metastatic bile duct cancer (cholangiocarcinoma) with FGFR2 fusion or rearrangement who have failed previous treatment. Advanced cholangiocarcinoma begins in the bile duct but spreads to other parts of the body and often is not diagnosed until a late stage. Symptoms of cholangiocarcinoma include yellowing of the skin and whites of eyes (jaundice), itchy skin, dark urine, loss of appetite, persistent tiredness, abdominal pain, fever, chills and shivering. The causes of cholangiocarcinoma are not yet fully understood but include smoking, obesity and alcohol consumption.

Pemigatinib is administered orally and it works by blocking receptors (targets) called fibroblast growth factor receptor (FGFR). FGFRs are found in many cancer cells and play a key role in the growth and spread of the cancer cells. By blocking the FGFR, pemigatinib is expected to reduce the growth and spread of the cancer. If licensed, pemigatinib may offer an additional treatment option for patients with locally advanced or metastatic cholangiocarcinoma with FGFR2 fusion or rearrangement who have failed previous therapy.

PROPOSED INDICATION

Pemigatinib is indicated for the treatment of adults with locally advanced or metastatic cholangiocarcinoma with FGFR2 fusion or rearrangement that is relapsed or refractory after at least one line of systemic therapy.[a, 1]

TECHNOLOGY

DESCRIPTION

Pemigatinib belongs to a group of medicines called protein kinase inhibitors. It works by blocking enzymes known as protein kinases, particularly those that are part of receptors (targets) called fibroblast growth factor receptors (FGFRs).[2] Pemigatinib is an orally bioavailable inhibitor of the FGFR types 1, 2, and 3 (FGFR1/2/3)with potential antineoplastic activity.[3,4] FGFRs are receptor tyrosine kinases with a role in several biological processes such as regulation of development and tissue repair. Alterations in FGFRs such as amplifications, overexpression and mutations can lead to development or progression of cancer.[5] Pemigatinib binds to and inhibits proliferation in FGFR1/2/3 which may result in the inhibition of FGFR1/2/3 related signal transduction pathways. This inhibits proliferation in FGFR1/2/3 overexpressing tumour cells.[4]

Pemigatinib is in clinical development for the treatment of adults with locally advanced or metastatic cholangiocarcinoma with FGFR2 fusion or rearrangement that is relapsed or refractory after at least one line of systemic therapy. In the phase II trial (FIGHT-202; NCT02924376), patients receive pemigatinib by oral administration once a day in 3 week cycles.[1]

INNOVATION AND/OR ADVANTAGES

As of August 2018, no satisfactory methods are authorised in the EU by the European medicines agency (EMA) for the treatment of cholangiocarcinoma.[2] Therefore, pemigatinib may offer an additional treatment option for patients with advanced and unresectable cholangiocarcinoma.

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

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

Pemigatinib is currently in phase II development for the treatment of bladder cancer, solid tumours and colorectal cancer.[6,7]

Pemigatinib was granted an orphan designation in the EU in August 2018 for the treatment of biliary tract cancer.[2]

[a] Information provided by Incyte Corp

PATIENT GROUP

DISEASE BACKGROUND

Cancer of the bile duct (cholangiocarcinoma) is a rare type of cancer that mainly affects adults aged over 65. Bile ducts are small tubes that connect the liver and small intestine. They allow fluid called bile to flow from the liver through the pancreas where it helps with digestion. Cancer can affect any parts of these ducts. Cholangiocarcinoma is not normally found until a late stage when a cure is not possible. [8]

There are not usually any symptoms of bile duct cancer until it grows large enough to block the bile ducts. This can cause: yellowing of the skin and whites of eyes (jaundice), itchy skin, darkening of urine, loss of appetite, persistent tiredness, abdominal pain, high temperature, chills and shivering.[9]

The cause of bile cancer is not yet known but is thought that a combination of genetic and environmental factors influence a person's risk of developing cholangiocarcinoma.[10] Cancers occur when a build-up of mutations in critical genes allow cells to grow and divide uncontrollably to form a tumour. Researchers have investigated inherited variations in several genes as possible risk factors for cholangiocarcinoma. However, no specific inherited changes have been found to be a major risk factor. Several non-genetic risk factors for cholangiocarcinoma have been identified. These include a bile duct disease called primary sclerosing cholangitis, bile duct stones or cysts, smoking alcohol use, obesity and exposure to certain chemical toxins used in manufacturing.[11]

CLINICAL NEED AND BURDEN OF DISEASE

In England, in 2018-2019 there were 9,560 finished consultant episodes (FCE) for intrahepatic bile duct carcinoma (ICD-10 code C22.1), which resulted in 6,614 admissions and 31,601 FCE bed days.[12]

According to the National Cancer Intelligence Network (NCIN) Cancer Rare and Less Common Cancers report the incidence rate of cholangiocarcinoma in England in 2012/13 was 3.58 per 100,000 and the mortality rate was 3.64 per 100,000.[13]

The outlook for bile duct cancer depends on which part of the bile duct is affected and how far the cancer has spread. Around 30 out of 100 men will survive for 1 year or more after being diagnosed and 25 out of 100 women will survive for 1 year or more after being diagnosed. Around 5 out of 100 men and women will survive for 5 years or more after being diagnosed.[8]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Normally patients diagnosed with cholangiocarcinoma have a poor prognosis with restricted treatment options.[14] Surgery is currently the only curative treatment for patients with cholangiocarcinoma.[15] In patients whose tumour is unresectable the current standard of care is palliative chemotherapy, radiotherapy or stent insertion.[16]

CURRENT TREATMENT OPTIONS

As of August 2018 the EMA have stated that no chemotherapy medicines are authorised for the treatment of cholangiocarcinoma.[2]

The ESMO guidelines recommend the following drugs for palliative chemotherapy: [17]

- Gemcitabine/cisplatin is the reference chemotherapy regimen for good performance status (PS) 0-1 patients
- Gemcitabine monotherapy may be considered for PS 2 patients
- There is no established second-line chemotherapy regimen
- There is no established evidence to support the use of targeted therapies

Cancer research UK indicates that the following drugs are used for biliary tract cancer:[18]

- Gemcitabine and cisplatin combination therapy (most common)
- Oxaloplatin
- Gemcitabine
- Capecitabine
- Flurouracil
- Cisplatin

PLACE OF TECHNOLOGY

If licensed, pemigatinib will offer an additional treatment option for adults with locally advanced or metastatic cholangiocarcinoma with FGFR2 fusion or rearrangement that is relapsed or refractory after at least one line of systemic therapy.

CLINICAL TRIAL INFORMATION

Trial	**FIGHT-202, NCT02924376, INCB 54828-202**; adults aged 18 years and older; pemigatinib; phase II
Sponsor	Incyte Corporation
Status	Ongoing, not recruiting
Source of Information	Trial registry,[1] Press release,[19]
Location	6 EU countries (incl UK), USA and other countries
Design	Open-label, single-arm, multicentre study
Participants	n=146 enrolled;[b] aged 18 years and older; histologically or cytologically confirmed cholangiocarcinoma; radiographically measurable or evaluable disease per RECIST v1.1; tumour assessment for FGF/FGFR gene alteration status; documented disease progression after at least 1 line of prior systemic therapy; eastern cooperative oncology group (ECOG) performance status of 0 or 2; life expectancy ≥ 12 weeks. Patients were assigned to cohorts A (FGFR2 gene rearrangements/fusions), B (other FGF/FGFR gene alterations), or C (no FGF/FGFR gene alterations) and received pemigatinib until disease progression/unacceptable toxicity

[b] Information provided by Inctye Corp

Schedule	An oral dose of pemigatinib once a day for 2 consecutive weeks and 1 week off therapy until disease progression or unacceptable toxicity.
Follow-up	Up to 6 months
Primary Outcomes	Objective response rate (ORR) in patients assigned to cohort As based on RECIST v1.1 (Time Frame: Every 6 weeks for the first 2 cycles and every 9 weeks thereafter through end of treatment, up to 6 months).
Secondary Outcomes	[Time Frame : Up to 6 months] • ORR in patients assigned to cohorts B, A+B and C based on RECIST v1.1 • Duration or response (DOR) • Disease control rate (DCR) • Progression-free survival based on RECIST v1.1 • Overall survival • Safety and tolerability of pemigatinib as assessed by the frequency, duration and severity of adverse events.
Key Results	ORR in cohort A was 35.5% (95% CI, 26.5%–45.4%), with 3 complete responses; median DOR was 7.5 (95% CI, 5.7–14.5) months, DCR was 82% (95% CI, 74%–89%), median PFS and median OS were 6.9 months (95% CI, 6.2–9.6) and 21.1 months (95% CI, 14.8–not reached; OS not mature at cut off). In cohorts B and C, no patient achieved a response.
Adverse effects (AEs)	Most common adverse events (AEs) were hyperphosphatemia (60%; grade ⩾3, 0%), alopecia (49%; grade ⩾3, 0%), diarrhea (47%; grade ⩾3, 3%), fatigue (42%; grade ⩾3, 5%), nail toxicities (42%; grade ⩾3, 2%), and dysgeusia (40%; grade ⩾3, 0%). Hyperphosphatemia was managed with diet modifications, phosphate binders, if needed; diuretics or dose reductions/interruptions. Discontinuation, dose reduction and interruption due to AEs occurred in 9%, 14% and 42% of patients, respectively.
Expected reporting date	Results were presented as a Late Breaking Abstract at ESMO Congress Barcelona 2019.

ESTIMATED COST

The cost of pemigatinib is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE interventional procedures guidance. Selective internal radiation therapy for unresectable primary intrahepatic cholangiocarcinoma (IPG630). October 2018.
- NICE interventional procedures guidance. Photodynamic therapy for bile duct cancer (IPG134). July 2005.

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.

OTHER GUIDANCE

- European Society of Medical Oncology (ESMO). Biliary Cancer: ESMO Clinical Practice Guidelines. 2016.[17]
- British Society of Gastroenterology (BSG). BSG guidelines for the diagnosis and treatment of cholangiocarcinoma. 2012.[20]

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.

Incyte Biosciences UK does provide yearly updates directly to NIHRIO.

REFERENCES

1 Clinicaltrials.gov. *Efficacy and Safety of Pemigatinib in Subjects With Advanced/Metastatic or Surgically Unresectable Cholangiocarcinoma Who Failed Previous Therapy - (FIGHT-202). Trial ID:* Status: Recruiting. Available from: https://ClinicalTrials.gov/show/NCT02924376 [Accessed 21 November 2019].

2 European Medicines Agency (EMA). *EU/3/18/2066: Public summary of opinion on orphan designation: Pemigatinib for the treatment of biliary tract cancer.* 2018. Available from: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3182066 [Accessed 25 November 2019].

3 US National Library of Medicine. *Pemigatinib.* Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Pemigatinib [Accessed 21 November 2019].

4 National Cancer Institute (NCI). *NCI drug dictionary: pemigatinib.* Available from: https://www.cancer.gov/publications/dictionaries/cancer-drug/def/fgfr-inhibitor-incb054828 [Accessed 29 November 2019].

5 Katoh M. Fibroblast growth factor receptors as treatment targets in clinical oncology. *Nature Reviews Clinical Oncology*. 2019 2019/02/01;16(2):105-22. Available from: https://doi.org/10.1038/s41571-018-0115-y 10.1038/s41571-018-0115-y.

6 Clinicaltrials.gov. *Search for pemigatinib clinical trials; phase II and III.* Available from: https://clinicaltrials.gov/ct2/results?intr=Pemigatinib&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 21 November 2019].

7 Incyte. *Incyte Portfolio.* 2019. Available from: https://voteforpolicies.org.uk/ [Accessed 12 December 2019].

8 National Health Service (NHS). *Bile duct cancer overview.* Available from: https://www.nhs.uk/conditions/bile-duct-cancer/ [Accessed 21 November 2019].

9 American Cancer Society. *Signs and symptoms of bile duct cancer*. Available from: https://www.cancer.org/cancer/bile-duct-cancer/detection-diagnosis-staging/signs-symptoms.html [Accessed 21 November 2019].
10 Zabron A, Edwards RJ, Khan SA. The challenge of cholangiocarcinoma: dissecting the molecular mechanisms of an insidious cancer. *Disease Models & Mechanisms*. 2013;6(2):281. Available from: http://dmm.biologists.org/content/6/2/281.abstract 10.1242/dmm.010561.
11 Genetics Home Reference. *Cholangiocarcinoma*. Available from: https://ghr.nlm.nih.gov/condition/cholangiocarcinoma#genes [Accessed 21 November 2019].
12 NHS Digital. *Hospital Admitted Patient Care Activity, 2018-19: Diagnosis*. . Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2018-19 [Downloaded 04 November 2019].
13 AMMF The Cholangiocarcinoma Charity. *Cholangiocarcinoma mortality higher than incidence?* 2015. Available from: https://ammf.org.uk/2015/06/25/cholangiocarcinoma-mortality-higher-than-incidence/ [Accessed 22 November 2019].
14 Woradet S, Songserm N, Promthet S, Parkin DM. Health-Related Quality of Life and Survival of Cholangiocarcinoma Patients in Northeastern Region of Thailand. *PloS one*. 2016;11(9):e0163448-e. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5042427/ 10.1371/journal.pone.0163448.
15 National Institute for Health and Care Excellence (NICE). *Search for cholangiocarcinoma guidance*. Available from: https://www.nice.org.uk/search?q=cholangiocarcinoma [Accessed 22 November 2019].
16 National Health Service (NHS). *Treatment of bile duct cancer (cholangiocarcinoma)*. 2019. Available from: https://www.nhs.uk/conditions/bile-duct-cancer/treatment/ [Accessed 29 November 2019].
17 Valle JW, Borbath I, Khan SA, Huguet F, Gruenberger T, Arnold D, et al. Biliary cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. *Annals of Oncology*. 2016;27(suppl_5):v28-v37. Available from: https://doi.org/10.1093/annonc/mdw324 10.1093/annonc/mdw324.
18 UK CR. *Bile duct cancer: Chemotherapy for advanced cancer*. 2018. Available from: https://www.cancerresearchuk.org/about-cancer/bile-duct-cancer/advanced/chemotherapy/treatment [Accessed 29 November 2019].
19 Incyte. *Incyte Announces Positive Interim Data from Phase 2 Trial of Pemigatinib, Its Selective FGFR Inhibitor, in Patients with Cholangiocarcinoma*. 2018. Available from: https://investor.incyte.com/news-releases/news-release-details/incyte-announces-positive-interim-data-phase-2-trial-pemigatinib [Accessed 06 December 2019].
20 British Society of Gastroenterology (BSG). *BSG guidelines for the diagnosis and treatment of cholangiocarcinoma*. 2012. Available from: https://www.bsg.org.uk/resource/bsg-guidelines-for-the-diagnosis-and-treatment-of-cholangiocarcinoma.html [Accessed 25 November 2019].

NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.