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HEALTH TECHNOLOGY BRIEFING
AUGUST 2021

Infigratinib for unresectable locally advanced or metastatic cholangiocarinoma with FGFR2 rearrangements – second line

NIHRIO ID	12434	**NICE ID**	10675
Developer/Company	QED Therapeutics	**UKPS ID**	N/A

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

SUMMARY

Cholangiocarcinoma (CCA) is a rare type of cancer that affects the bile ducts. Locally advanced CCA is when the cancer spreads from its original site to surround areas, but has not spread to other parts of the body. Metastatic CCA is when the cancer has spread to other areas of the body. Current treatment options for patients with locally advanced and metastatic CCA, who have progressed following chemotherapy are limited.

Infigratinib is an oral capsule that is taken once daily every three out of four weeks. It works by targeting fibroblast growth factor receptor 2 (FGFR2) mutations, which commonly promote cancer growth and spread, by doing so it inhibits this process. Infigratinib is in development for people who have inoperable locally advanced or metastatic CCA with the presence of FGFR2 mutations. If licenced infigratinib would offer a second line or greater treatment option for these patients.

PROPOSED INDICATION

Infigratinib is indicated for adults with previously treated, unresectable locally advanced or metastatic CCA with a FGFR2 fusion or other rearrangement.[1]

TECHNOLOGY

DESCRIPTION

Infigratinib (Truseltiq; BGJ398) is a small molecule kinase inhibitor of FGFR, which targets FGFR1/2/3/4.[2] FGFR signalling can support the proliferation and survival of malignant cells.[2-5] Infagritinib inhibits this FGFR signalling and decreases cell proliferation in cancer cell lines with activating FGFR amplifications, mutations or fusions.[2]

Infigratinib is currently in phase II clinical development (NCT02150967) for adult patients with advanced or metastatic cholangiocarcinoma with FGFR2 gene fusions or other FGFR genetic alterations who failed or are intolerant to platinum-based chemotherapy.[6] Patients will receive 125mg of infigratinib as an oral capsule once daily for 21 days, then 7 days off (28-day cycles).[7]

INNOVATION AND/OR ADVANTAGES

Treatment options are sparse for patients with advanced cholangiocarcinoma after progression on first-line gemcitabine-based therapy. In a phase II clinical trial (NCT02150967) infigratinib was associated with promising anticancer activity and a manageable adverse event profile in patients with advanced, refractory CCA with FGFR2 gene fusion or rearrangement.[7]

The adverse effect profile of infigratinib was comparable to that of pemigatinib, another FGFR inhibitor, though there are no direct data comparisons between FGFR inhibitors. Infigratinib is an ATP-competitive inhibitor very specific for FGFR1, FGFR2, and FGFR3. It has much less FGFR4 activity compared with some of the other agents, such as pemigatinib and futibatinib, and is very potent for FGFR2.[8]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

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

Infigratinib is also in phase II and III clinical development for the following:[9]

- Invasive urothelial carcinomas
- Recurrent head and neck cancer
- Achondroplasia

Infigratinib has the following regulatory designations:

- In August 2020, infigratinib was granted Orphan Drug Designation by the EMA for the treatment of CCA.[10]

- In January 2020, infigratinib was granted US FDA Fast Track Designation and Orphan Drug Designation for first line treatment in adults with advanced or metastatic CCA.[11]
- In December 2020, infigratinib was granted US FDA Priority Review for the treatment of CCA.[12]
- In May 2021, infigratinib was granted accelerated approval by the US Food and Drug Administration (FDA) for adults with previously treated, unresectable locally advanced or metastatic CCA with a FGFR2 fusion or other rearrangement.[1,13]

PATIENT GROUP

DISEASE BACKGROUND

Cholangiocarcinoma (CCA), cancer of the bilary tract, is a rare type of cancer that mainly affects adults aged over 65 years.[14] Bile ducts are small tubes that connect the gall bladder, liver and small intestine.[15] 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. CCA is not normally found until a late stage when a cure is not possible.[14] CCA types are classified by the location at which they develop in the biliary tract, these vary in biological behaviour and management, and are called intrahepatic and extrahepatic.[16] FGFR2 mutations occur in 13-17% of intrahepatic CCA.[7]

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, lightening of stools, loss of appetite, persistent tiredness, abdominal pain, high temperature, and shivering.[14,15]

The cause of bile cancer is not known, but is thought that a combination of genetic and environmental factors influence a person's risk of developing CCA.[17] 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 CCA. However, no specific inherited changes have been found to be a major risk factor.[18] Several non-genetic risk factors for CCA have been identified including parasitic infection and exposure to toxins. Other factors that may increase the risk of developing bile duct cancer, but where more research is needed, includes hepatitis B or C, cirrhosis, HIV, diabetes, obesity and smoking.[19]

Locally advanced cancer is where the cancer has grown outside of the area it originated from, but has not spread to other parts of the body and cannot be cured. Metastatic cancer has spread to other areas of the body and can be advanced (incurable), but not necessarily all metastatic cancers are advanced.[20] Unresectable (inoperable) cancer cannot be removed by surgery due to their placement or distribution in the body.[21]

People with CCA have a poor prognosis, short-term survival and lower quality of life (QoL).[22-24] There are a number of health-related quality of life (HRQoL) studies, however they are often from a heterogeneous patient population, and not consistently specified for CCA stage or subtype.[24] There is are signs that patients with higher HQoL show more favourable outcomes, such as improved survival, with QoL improving with therapy.[22,23] Some studies include patient

symptom reporting, including but not limited to, gastrointestinal distress, abdominal pain, fatigue, fever, itching, difficulty sleeping, anxiety, jaundice and weight loss.[24]

In a recent survey by Incyte and the Cholangiocarcinoma Foundation, 35% of 707 patients received an initial misdiagnosis, of which the most common misdiagnosis was gall bladder cancer. Patients reported negative life impact from anxiety, tiredness and treatment; with 58% of patients reporting that depression made their daily life difficult.[25]

CLINICAL NEED AND BURDEN OF DISEASE

In England, in 2019-20, there were 10,656 finished consultant episodes (FCE) for intrahepatic bile duct carcinoma (ICD-10 code C22.1, which includes CCA)[26], which resulted in 4,668 day cases and 35,791 FCE bed days.[27]

According to the National Cancer Intelligence Network's (NCIN) Rare and Less Common Cancers report the crude incidence rate of CCA in England in 2013 was 3.65 per 100,000, and crude mortality rate was 4.01 per 100,000.[26]

There are no UK-wide statistics available for CCA survival. However the following survival of 1 year or more after diagnosis statistics are provided by the NCIN. This is people in England, in 2012, diagnosed with billary tract cancer for all stages:[28]

- Almost 30 out of 100 men (almost 30%)
- 25 out of 100 women (25%) survived 1 year or more after diagnosis

The 5 year or more survival rate after diagnosis for people in England, in 2008, diagnosed with billary tract cancer for all stages was:[28]

- More than 5 out of 100 men (more than 5%)
- Around 5 out of 100 women (around 5%)

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Chemotherapy may be used to make the cancer smaller, and control and improve symptoms if surgery is not possible. Radiotherapy may be offered after surgery to help prevent recurrence, and control and improve symptoms of advanced cancer. Chemotherapy and radiotherapy can also be used in combination.[29,30]

CURRENT TREATMENT OPTIONS

For metastatic or advanced CCA patients who have already received first line treatment of combination chemotherapy (gemcitabine/cisplatin), the second line treatment is folinic acid, fluorouracil and oxaliplatin (FOLFOX).[30]

PLACE OF TECHNOLOGY

If licenced infigratinib would provide a second line or greater treatment option for adults with previously treated, unresectable locally advanced or metastatic CCA with a FGFR2 fusion or other rearrangement.

CLINICAL TRIAL INFORMATION

Trial	NCT02150967; 2013-005085-19; A Phase II Multicenter, Single Arm Study of Oral BGJ398 in Adult Patients With Advanced or Metastatic Cholangiocarcinoma With FGFR2 Gene Fusions or Other FGFR Genetic Alterations Who Failed or Are Intolerant to Platinum-based Chemotherapy **Phase II –** Recruiting **Location(s):** 4 EU countries, UK, United States, and other countries **Primary completion date:** March 2022
Trial design	Open label, single group assignment.
Population	N= 160 (estimated); aged 18 years or older; with confirmed CCA; received at least one prior regimen containing gemcitabine with or without cisplatin for advanced/metastatic disease; with evidence of progressive disease following prior regimen, or if prior treatment discontinued due to toxicity must have continued evidence of measurable or evaluable disease
Intervention(s)	Patients will receive 125mg of infigratinib as an oral capsule once daily for 21 days, then 7 days off (28-day cycles).[7]
Comparator(s)	No comparator.
Outcome(s)	Overall response rate (ORR) [Time Frame: up to 24 months] Overall response rate (ORR) is defined as the proportion of patients with a best overall response of Complete Response (CR) or Partial Response (PR), as per RECIST version 1.1. See trial record for full list of other outcomes.
Results (efficacy)	Median follow-up was 10.6 months (range 1.1–55.9 months). 96 patients (88.9%) discontinued treatment (12 ongoing). Centrally reviewed ORR was 23.1% (95% CI 15.6–32.2) including 1 CR and 24 PRs; median DOR was 5.0 months (range 0.9–19.1 months). Among responders, 8 (32.0%) patients had a DOR of ⩾6 months. Median PFS was 7.3 months (95% CI 5.6–7.6 months). ORR was 34% (17/50) in the second-line setting and 13.8% (8/58) in the third-/later-line setting (3–8 prior treatments).[7]
Results (safety)	Most common treatment-emergent adverse events (TEAEs, any grade) were hyperphosphatemia (76.9%), eye disorders (67.6%, excluding central serous retinopathy/retinal pigment

	epithelium detachment [CSR/RPED]), stomatitis (54.6%), and fatigue (39.8%).[7]

ESTIMATED COST

The estimated cost of infigratinib is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE guidance in development. Pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 alterations (ID3740). Expected publication date: August 2021.
- NICE interventional procedures guidance. Selective internal radiation therapy for unresectable primary intrahepatic cholangiocarcinoma (IPG630). Publication date: October 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.

OTHER GUIDANCE

- European Society of Medical Oncology (ESMO). Biliary Cancer: ESMO Clinical Practice Guidelines. 2016.[31]
- British Society of Gastroenterology (BSG). BSG guidelines for the diagnosis and treatment of cholangiocarcinoma. 2012.[32]

ADDITIONAL INFORMATION

QED Therapeutics 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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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.