Health Technology Briefing
July 2022

Ivosidenib for previously treated advanced cholangiocarcinoma

Company/Developer	Servier Laboratories Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 19362	NICE TSID: 10360	UKPS ID: 665057

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Cholangiocarcinoma is a rare type of cancer that affects the bile ducts. Different subtypes of cholangiocarcinoma are classified by the location at which they develop in the biliary tract. Genetic changes (mutations) to the metabolic enzyme isocitrate dehydrogenase 1 (IDH1) plays a central role in development of cholangiocarcinoma by contributing to the growth of abnormal cancerous cells. Currently there are limited treatment options for advanced or metastatic (where the cancerous cells have spread to other areas of the body) IDH1 gene-mutated cholangiocarcinoma and the prognosis for these patients remains poor.

Ivosidenib (AG-120) is an oral tablet taken daily that targets the mutated form of IDH1 and prevents the formation of 2-hydroxyglutarate (2HG), thereby reducing the growth of cancerous cells. Ivosidenib is in clinical development for treatment of previously treated advanced or metastatic cholangiocarcinoma with an IDH1 gene mutation. If licensed, ivosidenib would offer as a novel second or third-line treatment option for patients.

Proposed Indication

Adult patients with locally advanced or metastatic cholangiocarcinoma with an isocitrate dehydrogenase-1 (IDH1) mutation, who received at least 1 and no more than 2 prior regimens of systemic therapy.[1]

Technology

Description

Ivosidenib (AG-120) is an orally available inhibitor of isocitrate dehydrogenase type 1 (IDH1), with potential antineoplastic activity. It specifically inhibits a mutated form of IDH1 in the cytoplasm, which inhibits the formation of the oncometabolite, 2-hydroxyglutarate (2HG). This leads to both an induction of cellular differentiation and an inhibition of cellular proliferation in IDH1-expressing tumour cells. IDH1, an enzyme in the citric acid cycle, is mutated in a variety of cancers; it initiates and drives cancer growth by both blocking cell differentiation and catalyzing the formation of 2HG.[2]

Ivosidenib is currently in clinical development for previously treated advanced cholangiocarcinoma with IDH1 mutations. In the phase III clinical trial (NCT02989857), patients are given a 500mg tablet orally once daily in each 28-day treatment cycle until occurrence of disease progression, unacceptable toxicity, confirmed pregnancy, death, subject withdrawal, or lost to follow-up, up to approximately 24 months.[1]

Key Innovation

Cholangiocarcinomas are rare, aggressive tumours, with an increasing incidence and poor prognosis.[3] Mutations of IDH1 play a central role in cholangiocarcinoma pathogenesis. Current treatment options for cholangiocarcinoma are for specific molecularly defined subsets of cholangiocarcinoma (e.g., cholangiocarcinoma with fibroblast growth factor receptor [FGFR] fusions, with neurotrophic tyrosine receptor kinase fusions, or microsatellite instability-high cancer). IDH1 mutated cholangiocarcinoma subtypes are rarely targeted, despite elevated 2-HG levels being implicated in epigenetic alterations and impaired cellular differentiation in an array of hematologic malignancies and solid tumors.[3,4] Currently, there is only 1 approved targeted treatment option for patients with unresectable and metastatic cholangiocarcinoma, highlighting the need for additional treatment options.[3]

If licensed, ivosidenib will provide a novel second or third-line treatment option for previously treated advanced cholangiocarcinoma with IDH1 mutation.

Regulatory & Development Status

Ivosidenib does not currently have marketing authorisation in the EU/UK for any indication.

Ivosidenib is currently in phase II/III clinical development for other indications with IDH1 mutations, including:[5]

- Clonal cytopenia
- Solid tumours
- Acute myeloid leukemia
- High risk myeloproliferative neoplasm
- Hematopoietic and lymphoid system neoplasm

Ivosidenib has the following regulatory awards/designations:

- An approved status by the U.S. FDA for treatment of advanced or metastatic cholangiocarcinoma in August 2021.[6]

Patient Group

Disease Area and Clinical Need

Bile duct cancer, also called cholangiocarcinoma, is a cancer that is found anywhere in the bile ducts. The bile ducts are small tubes that connect different organs. They are part of the digestive system.[7] Cholangiocarcinoma types (intrahepatic, perihilar or distal extrahepatic) are classified by the location at which they develop in the biliary tract, these vary in biological behaviour and management.[8] Mutations in the metabolic enzyme IDH1 play a central role in cholangiocarcinoma pathogenesis and are detected in approximately 13% of intrahepatic and 1% of extrahepatic cholangiocarcinomas.[3] Mutant IDH (mIDH) enzymes participate in many cellular processes such as histone and DNA demethylation, and adaption to hypoxia, and their inhibition leads to a block in normal cellular differentiation and oncogenic transformation.[4] Advanced cancer refers to cancers that have grown outside of the area it originated from, but have 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.[9] Cholangiocarcinoma does not usually cause signs or symptoms until later in the course of the disease, however symptoms can include: yellowing of the skin/whites of the eyes, itchy skin, dark urine, loss of appetite, nausea, high temperature and shivering.[7,10] Risk factors that increase the likelihood of cholangiocarcinoma include: being over the age of 65, have certain medical conditions, such as abnormal bile ducts, long term swelling in the bowel (ulcerative colitis) or bile ducts, a parasite in the liver (liver flukes), bile duct stones and liver cirrhosis.[11]

According to the National Cancer Intelligence Network's (NCIN) Rare and Less Common Cancers report the crude incidence rate of cholangiocarcinoma in England in 2013 was 3.65 per 100,000, and crude mortality rate was 4.01 per 100,000.[12] In England (2020-21), there were 8,914 finished consultant episodes (FCEs) and 6,408 admissions for Malignant neoplasm: Intrahepatic bile duct carcinoma (ICD-10 code C22.1), which resulted in 4,097 day cases and 25,034 FCE bed days.[13]

Recommended Treatment Options

NICE recommends pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 fusion or rearrangement in adults.[14]

Clinical Trial Information

Trial	**ClarIDHy,** NCT02989857; A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-controlled Study of AG-120 in Previously-treated Subjects With Nonresectable or Metastatic Cholangiocarcinoma With an IDH1 Mutation **Phase III:** Completed **Location(s):** 3 EU countries, UK, USA and Republic of Korea. **Actual study completion date:** May 2021
Trial Design	Randomized, parallel assignment, double masking, placebo controlled
Population	N=187; 18 years and older; histopathological diagnosis of nonresectable or metastatic cholangiocarcinoma and are not eligible for curative resection, transplantation, or ablative therapies; documented IDH1 gene-mutated disease;

	at least one evaluable and measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1; documented disease progression following at least 1 and no more than 2 prior systemic regimens for advanced disease (nonresectable or metastatic)
Intervention(s)	Oral dose of AG-120 500 mg tablet once daily (QD) in each 28-day treatment cycle, until occurrence of disease progression, unacceptable toxicity, confirmed pregnancy, death, subject withdrawal, lost to follow-up, or the sponsor ended the study for up to approximately 24 months.
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome(s): • Progression Free Survival (PFS) as Determined by the Independent Radiology Committee (IRC) [time frame: from the date of randomization to the date of first documentation of disease progression or death due to any cause (up to approximately 2 years)] See trial record for full list of outcomes
Results (efficacy)	This randomized clinical trial found that ivosidenib was well tolerated and resulted in a favorable overall survival benefit vs placebo, despite a high rate of crossover. Progression-free survival was significantly improved with ivosidenib compared with placebo (median 2·7 months [95% CI 1·6–4·2] vs 1·4 months [1·4–1·6]; hazard ratio 0·37; 95% CI 0·25–0·54; one-sided p<0·0001).[3,15]
Results (safety)	The most common grade 3 or higher treatment-emergent adverse event (≥5%) reported in both groups was ascites (11 patients [9%] receiving ivosidenib and 4 patients [7%] receiving placebo). Serious treatment-emergent adverse events considered ivosidenib related were reported in 3 patients (2%). There were no treatment-related deaths. Patients receiving ivosidenib reported no apparent decline in quality of life compared with placebo.[15]

Estimated Cost

The estimated cost of Ivosidenib is not yet known.

Relevant Guidance

NICE Guidance

- NICE guidance in development. Pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 alterations (ID3740). August 2021.
- NICE interventional procedures guidance. Selective internal radiation therapy for unresectable primary intrahepatic cholangiocarcinoma (IPG630). 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.[16]
- British Society of Gastroenterology (BSG). BSG guidelines for the diagnosis and treatment of cholangiocarcinoma. 2012.[17]

Additional Information

The preferred regulatory strategy is currently under discussion and scientific advice has been requested. The European Commission Decision Reliance Procedure (ECDRP) is the preferred option if still available.

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