NIHR | Innovation Observatory

HEALTH TECHNOLOGY BRIEFING
MAY 2021

Ripretinib for gastrointestinal stromal tumour

NIHRIO ID	26756	**NICE ID**	10431
Developer/Company	Deciphera Pharmaceuticals LLC	**UKPS ID**	Not Available

Licensing and market availability plans	Currently in phase III clinical development.

SUMMARY

Ripretinib is currently in clinical development for the treatment of gastrointestinal stromal tumours (GIST). GIST is a rare type of cancer that commonly develops in the gastrointestinal tract. The cause of GIST is unknown, but most cases are associated with a certain gene mutation that produces abnormal enzymes. GIST are very aggressive, can spread quickly to other parts of the body (metastatic) and are not easily removed surgically (unresectable). There are currently no approved therapies for patients with GIST who are resistant to imatinib.

Ripretinib is a drug orally administered to stop the abnormal and overactive enzymes in GIST cells from working, including forms that cannot be blocked by other medicines. Stopping these enzymes is expected to slow down the growth of the tumours and reduce symptoms of the disease. If licensed, ripretinib will offer a second-line treatment option for patients with unresectable or metastatic GIST who were resistant to imatinib.

PROPOSED INDICATION

Treatment for patients with advanced gastrointestinal stromal tumour (GIST) who were resistant to imatinib.[1]

TECHNOLOGY

DESCRIPTION

Ripretinib (DCC-2618, Qinlock) is a switch-control inhibitor of tyrosine-protein kinase (KIT) and platelet derived growth factor alpha (PDGFRα) kinase that works at the juxtamembrane domain (JMD) and the main activation loop switch. Ripretinib restores the inhibitory JMD switch, which is often deactivated in GIST, and helps to stabilise the kinase in an inactive state.[2] Ripretinib blocks initiating KIT mutations in exons 9, 11, 13, 14, 17, and 18, known to be present in GIST patients, and PDGFRα mutations in exon 18, including the D842V mutation that drives a subset of GIST.[3]

Ripretinib also inhibits several other kinases, including vascular endothelial growth factor receptor type 2, angiopoietin-1 receptor, PDGFR-beta and macrophage colony-stimulating factor 1 receptor, thereby further inhibiting tumour cell growth.[4]

Ripretinib is currently in clinical development for patients with advanced GIST who have been previously treated with imatinib. In the phase III clinical trial (NCT03673501, Intrigue), participants are given 150mg of ripretinib orally for 6 weeks.[1]

INNOVATION AND/OR ADVANTAGES

Evidence suggests that response to imatinib is not experienced by all patients, and most patients with GIST will ultimately develop resistance to imatinib, most commonly due to the development of secondary mutations in KIT.[5] Ripretinib was specifically designed to improve the treatment of GIST patients by inhibiting the full spectrum of known mutations in KIT.[3]

The Food and Drug Administration's approval of ripretinib for GIST patients after progression to imatinib, sunitinib and regorafenib constitutes a major breakthrough in sarcoma drug development, as there have not been new treatment approvals in GIST for nearly a decade.[6]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

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

On May 15, 2020, the Food and Drug Administration approved, for adult patients with advanced GIST who have received prior treatment with 3 or more kinase inhibitors, including imatinib.[7]

Ripretinib is also in phase I clinical development for advanced systemic mastocytosis and advanced cancers.[8]

PATIENT GROUP

DISEASE BACKGROUND

A GIST is a rare type of sarcoma found in the digestive system, most often in the wall of the stomach. A soft tissue sarcoma is a type of cancer.[9] They account for 18% of all sarcomas.[10] GIST can arise anywhere along the gastrointestinal tract, but most commonly occur in the stomach, small intestine, and less frequently in the rectum, oesophagus, or elsewhere in the abdominal cavity.[11] GIST are aggressive tumours that have historically portended a poor prognosis. In advanced GIST the tumours have begun to spread to other parts of the body, commonly spread to the liver and peritoneum.[12] Median survival in metastatic GIST is approximately 9 months given its inherent chemotherapy and radiation resistance.[13] The majority of GIST cases (82-87%) are characterised by the presence of mutations in PDGFRα and KIT.[14]

The causes of GISTs are unknown.[15] GISTs are usually found in adults between ages 40 and 70 years; rarely, children and young adults develop these tumours. Most cases of GIST are not inherited.[16]

The symptoms depend on the size of the tumour and where it is in the digestive system. Symptoms may include discomfort or pain in the abdomen, blood in the stools or vomit, anaemia, a painless lump in the stomach, vomiting, fatigue, fever and sweating at night, and unexplained weight loss.[15]

CLINICAL NEED AND BURDEN OF DISEASE

Every year, about 900 people in the UK are diagnosed with a GIST.[15] In 2019-2020 there were 8,880 finished consultant episodes of malignant neoplasm of other connective and soft tissue (ICD: 0 code C49) of which GIST is a subcategory. There were also 8,222 admissions (of which 4,336 were day cases).[17]

Approximately half of new cases of GIST are likely to be advanced on first presentation and approximately 50% of GISTs recur by 5 years after complete resection, making it a life threatening condition.[12] According to the American Cancer Society, the overall relative 5-year survival rate of people diagnosed with a malignant GIST between 2010 and 2016 was estimated to be about 83%. The 5-year relative survival if the tumour was localised (limited to original organ) compared to if it had spread to distant parts of the body at first diagnosis was 93% and 55% respectively.[18] In 2017, there were 1,661 registered deaths for ICD 10 code: C49.[19]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The treatment for GIST depends on several factors, including the general health of patient and the size and location of the tumour. GIST patients should be referred to a specialist unit for treatment. Surgery may be used to treat GISTs that come back after treatment. Drugs known as growth inhibitors are used to treat GISTs in patients that cannot be removed with surgery.[9]

CURRENT TREATMENT OPTIONS

The following pharmacological treatment options for unresectable or metastatic GIST are recommended by NICE:[5]

- Imatinib as first-line management of people with KIT (CD117)-positive unresectable and/or KIT (CD117)-positive metastatic GIST
- Sunitinib as a treatment option for people with unresectable and/or metastatic GISTs that are imatinib resistance or intolerance
- Regorafenib as a treatment option (third line) for people with unresectable or metastatic GIST whose disease has progressed on, or who are intolerant to, prior treatment with imatinib and sunitinib, only if their Eastern Cooperative Oncology Group (ECOG) performance status is 0 to 1.
- Genomic biomarker-based treatment for solid tumours.

PLACE OF TECHNOLOGY

If licensed, ripretinib will offer a second-line treatment option for patients with advanced GIST.

CLINICAL TRIAL INFORMATION

Trial	**Intrigue; NCT03673501;** A Phase 3, Interventional, Randomized, Multicenter, Open-Label Study of DCC-2618 vs Sunitinib in Patients With Advanced Gastrointestinal Stromal Tumors After Treatment With Imatinib **Phase III** – Active, not recruiting **Location(s):** EU (including UK) , Canada, United States, and other countries **Estimated primary completion date:** June 2021
Trial design	Randomised, parallel-assignment, open-label, multicentre
Population	N = 426, aged 18 years or older, histologic diagnosis of GIST and must be able to provide an archival tumour tissue sample, patients must have progressed on imatinib or have documented intolerance to imatinib.
Intervention(s)	150mg oral ripretinib

Comparator(s)	50mg oral sunitinib
Outcome(s)	Progression free survival (PFS) [Time frame: 30 months]
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The cost of ripretinib is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Ripretinib for treating advanced gastrointestinal stromal tumours after 3 therapies. (GID-TA10671). Expected May 2022.
- NICE technology appraisal in development. Avapritinib for treating unresectable or metastatic gastrointestinal stromal tumours. (GID-TA10523). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Gastrointestinal stromal tumours (unresectable, metastatic) - masitinib (after progression with imatinib) (GID-TAG360). Expected date of issue to be confirmed.
- NICE technology appraisal. Regorafenib for previously treated unresectable or metastatic gastrointestinal stromal tumours. (TA488). November 2017.
- NICE technology appraisal. Imatinib for the adjuvant treatment of gastrointestinal stromal tumours. (TA326). November 2014.
- NICE technology appraisal. Imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours. (TA209). November 2010.
- NICE technology appraisal. Sunitinib for the treatment of gastrointestinal stromal tumours. (TA179). September 2009.
- NICE quality standard. Sarcoma. (QS78). January 2015.

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: Soft Tissue Sarcoma (Adult). B12/S/a.

OTHER GUIDANCE

- European Society for Medical Oncology (ESMO). Gastrointestinal stromal tumours: ESMO–EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2018.[20]

ADDITIONAL INFORMATION

Deciphera Pharmaceuticals LLC 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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