

HEALTH TECHNOLOGY BRIEFING FEBRUARY 2020

Ripretinib for treating advanced gastrointestinal stromal tumours – fourth-line

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| NIHRIO ID | 13780 | NICE ID | 10042 |
| Developer/Company | Deciphera Pharmaceuticals LLC | UKPS ID | Not Available |

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| Licensing and market availability plans | Currently in phase III clinical trials. |
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SUMMARY

Ripretinib is currently in clinical development for the treatment of advanced 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 the majority of cases are associated with a certain gene mutations that produce 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 have exhausted treatment options with approved first, second, and third-line agents.

Ripretinib is a drug specifically designed 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 fourth-line treatment option for patients with unresectable or metastatic GIST who have exhausted all other approved treatment options.

PROPOSED INDICATION

Treatment of advanced gastrointestinal stromal tumours (GIST) – fourth-line.¹

TECHNOLOGY

DESCRIPTION

Ripretinib (DCC-2618) is a switch-control inhibitor of tyrosine-protein kinase (KIT) and platelet derived growth factor alpha (PDGFR α) 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 stabilize 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 PDGFR α 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 in clinical development for the treatment of patients with advanced GIST. In the phase III clinical trial (NCT03353753, INVICTUS) participants received 150mg of ripretinib oral tablets daily for 28 days cycles.^{1,5}

INNOVATION AND/OR ADVANTAGES

Despite advances in personalized therapies, there is still a significant unmet need, particularly in metastatic unresectable GIST as resistance to current therapies often develops. Currently approved kinase inhibitors that control certain initiating and drug resistance-causing mutations in KIT and PDGFR α , fail to inhibit all known mutations. Furthermore secondary mutations in KIT or PDGFR α eventually lead to drug resistance in most patients. Ripretinib was specifically designed to improve the treatment of GIST patients by potentially inhibiting the full spectrum of known mutations in KIT and PDGFR α including D842V.^{3,6}

Ripretinib is a novel therapy in a population with no other approved therapy and may represent a new standard of care.

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

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

Ripretinib was awarded an orphan designation in the EU in October 2017 for the treatment of GIST.⁷

In October 2019, the FDA granted Breakthrough Therapy Designation for ripretinib for the treatment of patients with advanced GIST who have received prior treatment with imatinib, sunitinib and regorafenib.⁸ In February 2020, the FDA accepted Priority Review for Ripretinib in patients with GIST.⁹

Ripretinib is currently in phase III clinical development for second-line treatment in GIST.¹⁰

PATIENT GROUP

DISEASE BACKGROUND

Gastrointestinal stromal tumours (GIST) are a form of soft tissue sarcoma (a rare cancer of mesenchymal origin), which develops in the digestive tract. They account for 18% of all sarcomas. 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. 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. Median survival in metastatic GIST is approximately 9 months given its inherent chemotherapy and radiation resistance.¹¹

The aetiology in most cases of GIST is unknown and does not seem to be linked to any particular diet or lifestyle although people with neurofibromatosis are at a slightly increased risk. They are most common in people aged 50 to 60 and are rare in people under the age of 40.¹² Familial GIST is also rare.¹³ In the majority of cases (over 85%), GIST is associated with an activating mutation in either the KIT or PDGFR α gene. PDGFR α is mutated in 5%–10% of GIST, with the PDGFR α D842V mutation accounting for ~60% of all PDGFR α mutations.¹⁴

Symptoms of GIST can vary depending on the size and location of the tumour and the early stages of the disease can be asymptomatic.¹⁵ Symptoms of advanced GIST may include fatigue, fever and sweating at night, discomfort or pain in the abdomen or around organs, a lump in the abdomen, feeling sick and vomiting, weight loss, blood in stools or vomit, and anaemia.^{12,13}

CLINICAL NEED AND BURDEN OF DISEASE

GIST is difficult to diagnose so estimates of the incidence vary widely, from 4 to 40 cases per million population, corresponding to between 200 and 2000 new cases per year in England and Wales.¹⁵ The estimated prevalence of third-line treatment-eligible GIST is 1/100,000 and fourth-line may be even lower, allowing the population to meet orphan status.¹⁶

In 2017 there were 1,661 diagnoses of malignant neoplasm of other connective and soft tissue (ICD 10 code C49) of which GIST is a subcategory.¹⁷ In 2018-19 there were 8,136 admissions (of which 5,170 were day cases) for primary diagnosis of malignant neoplasm of other connective and soft tissue (ICD-10 code C49) in England which resulted in 8,781 finished consultant episodes (FCE) and 20,791 FCE bed days.¹⁸

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.¹¹ According to the American Cancer Society, the overall relative 5-year survival rate of people diagnosed with a malignant GIST between 2009 and 2015 was estimated to be about 83%. The 5-year relative survival if the tumour was localized (limited to original organ) compared to if it had spread to distant parts of the body at first diagnosis was 94% and 52% respectively.¹⁹ In 2017 there were 829 registered deaths for ICD 10 code: C49.¹⁷

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.²⁰

CURRENT TREATMENT OPTIONS

The following pharmacological treatment options for unresectable or metastatic GIST are recommended by NICE:²¹

- 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.

In England, there are no other fourth-line therapies recommended by NICE for the treatment of patients with advanced GIST. ESMO guidelines also have no fourth-line therapy option however they do suggest rechallenge or continuation of treatment beyond progression with imatinib to which the patient has already been exposed.²²

PLACE OF TECHNOLOGY

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

CLINICAL TRIAL INFORMATION

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| Trial | INVICTUS; NCT03353753, 2017-002446-76 ; A Phase 3, Interventional, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of DCC-2618 In Patients with Advanced Gastrointestinal Stromal Tumours who have Received Treatment with Prior Anticancer Therapies Phase III - ongoing Location(s): EU (including UK), USA, Canada, Australia, and Singapore. |
| Trial design | Randomised, placebo-controlled, double-blind, crossover assignment |
| Population | N=129; advanced GIST; progression on imatinib, sunitinib, and regorafenib or have documented intolerance to any of these treatments; aged 18+ years. |
| Intervention(s) | Ripretinib tablet orally at a dose of 150 mg once a day in repeated 28-day cycles with best supportive care. |
| Comparator(s) | Matched placebo |
| Outcome(s) | Primary outcome: Progression free survival (PFS) based on independent radiologic review using modified RECIST [Time Frame: 15 months] See trial record for full list of other outcomes. |

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| Results (efficacy) | <p>Median PFS of 6.3 months (27.6 weeks) was observed in ripretinib treated subjects compared to 1.0 month (4.1 weeks) in the placebo arm and significantly reduced the risk of disease progression or death by 85% (HR of 0.15, p<0.0001) compared to placebo.</p> <p>Ripretinib demonstrated an objective response rate of 9.4% compared with 0% for placebo (p-value=0.0504), which was not statistically significant. A clinically meaningful improvement over placebo in terms of the secondary endpoint overall survival (OS) (median OS 15.1 months vs. 6.6 months, HR = 0.36, nominal p-value=0.0004) was observed with ripretinib treated subjects. Since statistical significance was not achieved for ORR, the hypothesis testing of OS was not formally performed.²³</p> |
| Results (safety) | <p>Ripretinib was generally well tolerated and the adverse event results in INVICTUS were consistent with data from previously presented Phase 1 study results. Grade 3 or 4 treatment-emergent adverse events (TEAEs) occurred in 42 (49%) patients on the ripretinib arm compared to 19 (44%) on the placebo arm. Grade 3 or 4 TEAEs >5% of patients in the ripretinib arm were anaemia (9%; n=8), abdominal pain (7%; n=6) and hypertension (7%; n=6). Grade 3 or 4 TEAEs >5% of patients in the placebo arm were anaemia (14%; n=6). The below table lists TEAEs >15% in the ripretinib arm compared to placebo.²³</p> |

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| Trial | <p>NCT02571036; A Multicenter Phase 1, Open-Label Study of DCC-2618 to Assess Safety, Tolerability, and Pharmacokinetics in Patients With Advanced Malignancies Phase I - ongoing Location(s): EU (incl UK), USA and Canada.</p> |
| Design | Non-randomised; parallel assignment; open-label |
| Population | N=320; Gastrointestinal Stromal Tumours, Advanced Systemic Mastocytosis and Advanced Cancers; aged 18+ years. |
| Intervention(s) | 150 mg ripretinib given once daily as 50 mg formulated tablets in repeated 28 day cycles. |
| Comparator(s) | No comparator |
| Primary Outcomes | <p>Primary outcome: Safety/tolerability of oral ripretinib: incidence of adverse events [Time frame: Approximately 24 months].</p> <p>See trial record for full list of other outcomes.</p> |
| Results (efficacy) | - |
| Results (safety) | - |

ESTIMATED COST

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| The cost of ripretinib is not yet known. |
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RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Gastrointestinal stromal tumours (unresectable, metastatic) - masitinib (after progression with imatinib) (GID-TAG360). Expected publication date to be confirmed.
- NICE technology appraisal in development. Avapritinib for treating unresectable or metastatic gastrointestinal stromal tumours [GID-TA10523] Expected publication date: 16 December 2020.
- 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. 2018.²²

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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