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NHS National Institute for Health Research

HEALTH TECHNOLOGY BRIEFING APRIL 2019

Avapritinib for unresectable or metastatic gastrointestinal stromal tumours (GIST) who have been treated with at least 3 prior lines of therapy and GIST harbouring the PDGFRA D842V mutation regardless of prior therapy

NIHRIO ID	26826	**NICE ID**	10159
Developer/Company	Blueprint Medicines Corp - GmbH	**UKPS ID**	Not available

Licensing and market availability plans	Currently in phase I clinical trial

SUMMARY

Avapritinib is currently in clinical development for the treatment of unresectable or metastatic 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, most commonly in the KIT or PDGFRA D842V genes. GIST with these mutations 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. In addition, no treatment options are approved specifically for patients with PDGRFA D842V–mutated GIST, which is resistant to all currently approved therapies.

Avapritinib is designed to potently and selectively inhibit the active forms of the KIT and PDGFRA mutant enzymes, and has shown potent activity in GIST driven by these gene mutations. If licensed, avapritinib will offer a fourth-line treatment option for patients with unresectable or metastatic GIST who have exhausted all other approved treatment options. It will also be the first licensed treatment option specifically for patients with unresectable or metastatic GIST harbouring a PDGRFA D842V mutation.

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.

PROPOSED INDICATION

Unresectable or metastatic gastrointestinal stromal tumours (GIST) who have been treated with at least 3 prior lines of therapy (fourth-line) and GIST harbouring the platelet-derived growth factor receptor alpha (PDGFRA) D842V mutation regardless of prior therapy.[a]

TECHNOLOGY

DESCRIPTION

Avapritinib (BLU-285) is a Type 1 kinase inhibitor that binds to the active conformation and inhibits a broad range of KIT and PDGFRA mutant kinases at clinically relevant concentrations. In in vitro biochemical assays, avapritinib inhibited the activity of KIT exon 11, 11/17 and 17 mutants and PDGFRA exon 18 mutants (D842V, D842I and D842Y), sparing activity on a range of other kinases including VEGFR2. Avapritinib has demonstrated biochemical in vitro activity on the KIT D816V and PDGFRA D842V mutants associated with resistance to imatinib, sunitinib and regorafenib with half maximal inhibitory concentrations (IC50) and greater potency against clinically relevant KIT exon 11 and KIT exon 17 mutants than against the KIT wild-type enzyme.[a]

Avapritinib is in clinical development for the treatment of patients with unresectable GIST and other relapsed or refractory advanced solid tumours with PDGFRA mutation. In the dose expansion (Part 2) of the NAVIGATOR study (NCT02508532), participants received a starting dose of either 300 or 400 mg of avapritinib oral tablets which will be dosed daily for 28 days cycles. Dose could be modified based on tolerability. The treatment should be continued until disease progression or unacceptable toxicity.[1,a]

INNOVATION AND/OR ADVANTAGES

Despite remarkable advances in personalized therapies, there is still a significant unmet need, particularly in metastatic unresectable GIST as resistance to current therapies often develops. Currently there are no approved therapies for PDGRFA D842V-driven GIST and no highly effective therapies for patients after failure with second line or greater.

Starting with a novel chemical library optimized for kinase selectivity and potency, avapritinib was identified as a small molecule kinase inhibitor that potently inhibits PDGFRα D842V mutant activity in vitro (IC50 = 0.5 nM) and PDGFRα D842V autophosphorylation in the cellular setting (IC50 = 30 nM).[2]

A clinical phase I study was performed as a dose-escalation study in patients with advanced unresectable GIST and advanced systemic mastocytosis. A patient with primary gastric PDGFRA D842V mutant GIST that was progressing under other tyrosine kinase inhibitors showed a drastic tumour size reduction after 8 weeks of daily orally administered avapritinib and after further 8 weeks, there was a rapid and sustained reduction in mutant allele load in blood plasma.[3]

The preliminary results of the NAVIGATOR study show that avapritinib has the potential to change GIST treatment paradigms. In particular, the updated data demonstrate the broad clinical impact of avapritinib for patients with PDGFRA D842V-driven GIST and fourth-line GIST, where there are currently no effective therapies.[4]

[a] Information provided by the Blueprint Medicines - GmbH

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

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

Avapritinib was awarded an orphan designation in the EU in July 2017 for the treatment of GIST.[5,6]

Avapritinib was granted breakthrough therapy designation from the FDA in June 2017 for the treatment of patients with unresectable or metastatic GIST harbouring the PDGFRA D842V mutation.[5,7]

Avapritinib is currently in phase III clinical development for other lines of treatment (second and third) in GIST.[5]

PATIENT GROUP

DISEASE BACKGROUND

Gastrointestinal stromal tumours (GIST) is a type of soft tissue sarcoma, (a rare cancer of mesenchymal origin), which develops in the digestive tract.[3,8,9] GISTs 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.[10] GISTs are aggressive tumours that have historically portended a poor prognosis.[11] Approximately 50% of GISTs recur by 5 years after complete resection. The tumour commonly spreads to the liver and peritoneum, and median survival in metastatic GIST was approximately 9 months given its inherent chemotherapy and radiation resistance.

Although the aetiology in most cases is unknown, they do not seem to be linked to any particular diet or lifestyle. They do not run in families except vary rarely. In the majority of cases, GIST is associated with an activating mutation in either the KIT or PDGFRA gene. PDGFRA is mutated in 5%–10% of GISTs, the PDGFRA D842V mutation accounting for ~60% of all PDGFRA mutations known in GISTs.[12] On the whole, mutations in the KIT and PDGFRA genes make the cancer cells always growing and dividing.[13]

Symptoms of GIST can vary depending on the size location of the tumour. They may include fatigue, fever and sweating at night, discomfort or pain in the abdomen or around organs, painless lump in the abdomen, feeling sick and vomiting, weight loss, blood in stools or vomit, and anaemia.[7,9]

CLINICAL NEED AND BURDEN OF DISEASE

Estimates of GIST incidence vary widely, from 4 to 40 cases per million population, which corresponds to between 200 and 2000 new cases per year in England and Wales.[14] Approximately 900 people are newly diagnosed with GIST in the UK each year.[15] Recent epidemiological data from Sweden suggests that the incidence of GIST is in the region of 15 per million per year. Approximately half of new cases of GIST are likely to be metastatic and/or unresectable on first presentation. Although GIST can occur at any age, the mean age of presentation is between 50 and 70 years.[14]

According to the American Cancer Society, the overall relative 5-year survival rate of people diagnosed with a malignant GIST between 2008 and 2014 was estimated to be about 83%. The 5-year relative survival if the tumour had grown into nearby structures (or spread to nearby lymph nodes), or spread to distant parts of the body when it was first diagnosed was 94% or 52% respectively.[16] Data from 21st Century Mortality dataset, England & Wales 2001–17 shows that there were 449 registered death for ICD 10 code: D37.[17]

In 2017-18 there were 7,855 admissions (of which 4,833 were day cases) for primary diagnosis of malignant neoplasm of other connective and soft tissue (ICD-10 code C49) in England which resulted in 8,424 finished consultant episodes (FCE) and 19,995 FCE bed days.[18]

Approximately 300 patients (1/3 of the new cases of GIST in UK) are likely to be metastatic and/or unresectable on first presentation and approximately 150 patients (50%) will progress on treatment with imatinib and be subsequently treated with sunitinib. Approximately 70% of patients receiving sunitinib will progress, with approximately 60% of them expected to subsequently receive regorafenib in the third-line setting. Regorafenib clinical efficacy is low, with an ORR of 4.5% and a median PFS of 4.8 months. It is expected that most patients treated with regorafenib would be eligible to receive avapritinib as a fourth-line therapy, i.e., approximately 55-60 patients per year in the UK.[b]

PDGFRA D842V-mutation GIST is extremely rare, representing 3-6% of GIST mutations. It can be estimated that 5 patients per year could be diagnosed with this form of GIST in UK and be eligible to avapritinib, irrespective of line of therapy.[b]

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.[9,19]

In England, there are no other lines of therapy recommended by NICE for the treatment of patients with unresectable or metastatic GIST whose disease has progressed upon treatment with regorafenib.[20] In addition, there are currently no approved therapies specifically for PDGRFA D842V-driven GIST.[b]

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

PLACE OF TECHNOLOGY

If licensed, avapritinib will offer a treatment option for patients with unresectable or metastatic GIST who have progressed or are intolerant to imatinib, sunitinib and regorafenib and will be the first licensed treatment option for patients with unresectable GIST who have PDGRFA D842V mutation, irrespective of line of therapy.

[b] Information provided by the Blueprint Medicines - GmbH

CLINICAL TRIAL INFORMATION

Trial	NAVIGATOR, NCT02508532, BLU-285-1101; avapritinib; phase I
Sponsor	Blueprint Medicines Corporation
Status	Ongoing
Source of Information	Trial registry, Blueprint Medicines - GmbH[c]
Location	EU (including the UK), United States and Republic of Korea
Design	Single group assignment, open-label. The study consists of 2 parts, a dose-escalation part (Part 1) and an expansion part (Part 2).
Participants[c]	At the time of the data cutoff date, a total of 237 patients have received at least 1 dose of avapritinib, including 46 patients in Part 1 (dose escalation) and 191 patients in Part 2 (expansion). The study enrolled patients of ≥18 years of age. Part 1: patients diagnosed with unresectable GIST or another advanced solid tumour, whose disease has progressed following imatinib and at least 1 of the following: sunitinib, regorafenib, sorafenib, dasatinib, pazopanib or an experimental kinase-inhibitor agent, or disease with a D842 mutation in the PDGFRA gene. To be eligible in the 3 groups in Part 2, patients must have had unresectable GIST and at least 1 measurable lesion defined by the mRECIST v1.1 in addition to the following inclusion criteria specific to each group: Part 2: Group 1: patients diagnosed with unresectable GIST whose disease has progressed following imatinib and at least 1 of the following: sunitinib, regorafenib, sorafenib, dasatinib, pazopanib or an experimental kinase-inhibitor agent, and the patient does not have a D842V mutation in PDGFRA. Group 2: patients must have had a D842V mutation in PDGFRA. Group 3 patients must have had progressed and/or have had experienced intolerance to imatinib and not have received additional kinase inhibitor therapy. Patients must not have had a known D842V mutation in PDGFRA.
Schedule[c]	In Part 1, patients received single oral avapritinib doses of 30 mg, 60 mg, 90 mg, 135 mg, 200 mg, 300 mg, 400 mg (MTD), and 600 mg. The dose administered to a patient was dependent upon which dose cohort was open for enrolment when the patient qualified for the study. Part 2 was initiated at the MTD of 400 mg, however based on the emerging data, 300 mg was chosen as the recommended dose.
Follow-up[c]	Patients received avapritinib until precluded by toxicity, noncompliance, withdrawal of consent, physician decision, progressive disease (PD), or death.
Primary Outcomes[c]	The primary efficacy endpoint was overall response rate (ORR), defined as the rate of confirmed complete response (CR) or partial response (PR) by central radiology per mRECIST v1.1 [time frame: at cycle 3 day 1, then every 2 cycles through cycle 13, then every 3 cycles thereafter]
Secondary Outcomes[c]	**Efficacy endpoints included**: • Duration of response [time frame: overall median and at 3, 6, and 12 months] • Progression-free survival [time frame: overall median and at 3, 6, and 12 months]

[c] Information provided by the Blueprint Medicines - GmbH

	• Clinical benefit rate [time frame: 16 weeks] • Response rate as defined by Choi Criteria [time frame: at cycle 3 day 1, then every 2 cycles through cycle 13, then every 3 cycles thereafter] • Median progression free survival (PFS) on last prior anti-cancer therapy [time frame: at cycle 3 day 1, then every 2 cycles through cycle 13, then every 3 cycles thereafter] **Exploratory efficacy endpoints included**: • Overall survival (OS) • Correlation of baseline KIT, PDGFRA, and other cancer relevant mutation status with antineoplastic activity. • Correlation of KIT, PDGFRA, and other cancer relevant mutant allele fractions in ctDNA with antineoplastic activity. • Time to response **Pharmacokinetics**: Serial blood samples were collected for determination of plasma concentrations of avapritinib, including metabolites, BLU111207 and BLU111208. Pharmacokinetic parameters included as appropriate: maximum plasma drug concentration (Cmax), time to maximum plasma drug concentration (Tmax), time of last quantifiable plasma drug concentration (Tlast), area under the plasma concentration-time curve from time 0 to 24 hours postdose (AUC0-24), plasma drug concentration at 24 hours postdose (C24); apparent volume of distribution (Vz/F), terminal elimination half-life (t½), apparent oral clearance (CL/F), accumulation ratio (R), and metabolite:parent ratio.
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Clinical Study Report 15 March 2019. [d]

ESTIMATED COST

The cost of avapritinib is not known yet.

ADDITIONAL INFORMATION

[d] Information provided by the Blueprint Medicines - GmbH

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.
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NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS STANDARD CONTRACT FOR CANCER: SOFT TISSUE SARCOMA (ADULT). B12/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/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]

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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.