NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
January 2023

Fruquintinib for treating refractory metastatic colorectal cancer

Company/Developer	Hutchmed Europe B.V

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 29686	NICE ID: 11843	UKPS ID: Not Available

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Fruquintinib is currently in clinical development for the treatment of refractory metastatic colorectal cancer (mCRC). Colorectal (or bowel) cancer starts in the large bowel (colon) and the back passage (rectum). The cause of colorectal cancer is unknown but various factors increase the risk of having it, including having a diet high in red or processed meats and low in fibre, smoking, and being overweight or obese. Metastatic cancer is cancer that has spread around the body from the place it had originally started from. Patients with mCRC have limited treatment options following progression on standard therapies, and treatment options include reuse of prior therapies. Therefore, there is an unmet medical need for additional safe and effective treatment.

Fruquintinib works by blocking some enzymes (proteins) known as tyrosine kinases that are found in proteins on the surface of cancer cells. These proteins are known as vascular endothelial growth factor (VEGF) receptors. VEGF receptors are involved in the growth and spread of cancer cells and in the development of blood vessels that supply the tumours. By blocking these receptors, fruquintinib helps to reduce the growth and spread of the cancer and cut off the blood supply that keeps the cancer cells growing. Fruquintinib is administered orally. If licenced, fruquintinib would provide an additional treatment option for patients with refractory mCRC.

Proposed Indication

Refractory metastatic colorectal cancer (mCRC).[1]

Technology

Description

Fruquintinib (HMPL-013) is a small-molecule inhibitor that targets the tyrosine kinase associated with VEGFR-1, VEGFR-2, and VEGFR-3. Inhibition of VEGFRs 1, 2, and 3 may result in the inhibition of migration, proliferation and survival of endothelial cells, microvessel formation, the inhibition of tumour cell proliferation, and tumour cell death. Expression of VEGFRs may be upregulated in a variety of tumour cell types.[2]

Fruquintinib is currently in clinical development for the treatment of refractory mCRC. In the phase III clinical trial (FRESCO-2, NCT04322539), patients are administered fruquintinib 5mg orally every day in addition to best supportive care for 3 weeks on, 1 week off in 28-day cycles.[1,3]

Key Innovation

The global outcome of mCRC is still poor and new therapies are needed. Small-molecule anti-VEGFR tyrosine kinase inhibitors (TKIs) have been shown to be effective in a variety of malignancies and are characterised by favourable oral bioavailability and the ability to target VEGFRs involved in tumour angiogenesis and growth. First-generation anti-VEGFR TKIs can inhibit VEGFR and other receptors involved in angiogenic signalling with similar potency. At the maximum tolerated dose (MTD), exposure of the multi-target TKI is limited. Since all targets are inhibited, the duration of inhibition for any target, particularly VEGFR, becomes less optimal and/or short. Thus, second-generation anti-VEGFR TKIs, such as fruquintinib, are characterised by potent and highly selective inhibition of VEGFR, which is expected to maintain target inhibition while minimising off-target toxicity and providing high drug exposure at the MTD.[4]

If licenced, fruquintinib would provide an additional treatment option for patients with refractory mCRC.

Regulatory & Development Status

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

Fruquintinib is also in phase II/III clinical development for various cancer indications, including:[5]

- Soft tissue sarcoma
- Rectal cancer
- Pancreatic cancer
- Non-small-cell lung cancer

Patient Group

Disease Area and Clinical Need

Colorectal cancer is type of bowel cancer that starts in the colon or rectum. The colon and rectum make up the large intestine. Colorectal cancer can also be called colon or rectal cancer, and are often grouped together due to the similar features they share in disease and organ function.[6] Metastatic cancer, also

known as Stage 4 cancer, is where the cancer has spread beyond the bowel into other areas of the body.[7] The main symptoms of bowel cancer are persistent blood in the stool, a persistent change in bowel habit, and persistent lower abdominal pain, bloating or discomfort. The exact cause of bowel cancer is not known but there are known risk factors including age (most prevalent in over 60's), diet, being overweight, consuming alcohol, smoking, and having a family history. Long term conditions such as ulcerative colitis and Crohn's disease can also increase risk.[8]

Bowel cancer is the 4th most common type of cancer in the UK, accounting for 11% of all new cancer cases (2016-18), and the 2nd most common cause of cancer death in the UK (2017-19).[9] The age standardised incidence rate of bowel cancer in England is 83.6 and 55.8 per 100,000 amongst males and females respectively (2016-18).[10] In England (2021-22), there were 178,203 finished consultant episodes (FCEs) and 162,089 admissions for colorectal cancer (ICD-10 codes C18-C20: malignant neoplasms of the colon, rectosigmoid junction, and rectum), which resulted in 125,188 day cases and 331,176 FCE bed days.[11] In the UK (2016-18) there were 42,886 new cases of bowel cancer and approximately 16,800 deaths each year (2017-19).[9] The one-year age standardised survival for adults diagnosed with Stage 4 colorectal cancer in England (2013-17) is 43.9%, whereas the five-year survival rate is 10.3%.[12]

Recommended Treatment Options

NICE currently recommends the following treatment options for previously treated mCRC:[13,14]

- Trifluridine-tipiracil
- Nivolumab with ipilimumab

Clinical Trial Information

Trial	**FRESCO-2, NCT04322539, 2020-000158-88;** A Global Multicenter Randomized Placebo-Controlled Phase 3 Trial To Compare The Efficacy And Safety Of Fruquintinib Plus Best Supportive Care To Placebo Plus Best Supportive Care In Patients With Refractory Metastatic Colorectal Cancer **Phase III** – Active, not recruiting **Locations:** 10 EU countries, UK, USA and other countries **Primary completion date:** July 2022
Trial Design	Randomised, parallel assignment, double-blind, quadruple-masked, placebo-controlled
Population	N=691 (actual); Patients with histologically and/or cytologically documented metastatic colorectal adenocarcinoma; have progressed on or been intolerant to treatment with either trifluridine/tipiracil (TAS-102) or regorafenib; aged 18 years and older
Intervention(s)	Fruquintinib (oral) 5mg every day + best supportive care, 3 weeks on, 1 week off in 28-day cycles.[3]
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome measure: • Overall survival [Time frame: up to 10 years]
Results (efficacy)	Fruquintinib significantly improved overall survival (OS) (median: 7.4 months (m) vs 4.8 m placebo (P); hazard ratio (HR)=0.66; [95% CI: 0.55, 0.80]; p<0.001) &

	progression-free survival (PFS) (median: 3.7 m vs 1.8 m P; HR=0.32; [95% CI: 0.27, 0.39]; p<0.001).[3]
Results (safety)	Grade ≥3 adverse events were 62.7% fruquintinib vs 50.4% P; those occurring in ≥5% on fruquintinib were hypertension (13.6% vs 0.9% P), asthenia (7.7% vs 3.9% P) & hand-foot syndrome (6.4% vs 0% P).[3]

Estimated Cost

The cost of fruquitinib is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Nintedanib for previously treated metastatic colorectal cancer (GID-TA10138). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Pembrolizumab with lenvatinib for previously treated metastatic colorectal cancer (GID-TA11020). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Regorafenib for previously treated metastatic colorectal cancer (GID-TA10924). Expected February 2023.
- NICE technology appraisal. Nivolumab with ipilimumab for previously treated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency (TA716). July 2021.
- NICE technology appraisal. Trifluridine–tipiracil for previously treated metastatic colorectal cancer (TA405). August 2016.
- NICE technology appraisal. Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer (TA118). January 2007; last updated January 2012.
- NICE guideline. Colorectal cancer (NG151). December 2021.
- NICE quality standard. Colorectal cancer (QS20). February 2022

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.

Other Guidance

- European Society for Medical Oncology (ESMO). Consensus guidelines for the management of patients with metastatic colorectal cancer. 2016.[15]
- Healthcare Improvement Scotland. SIGN 126. Diagnosis and management of colorectal cancer. 2016.[16]

Additional Information

Hutchmed Europe B.V. 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.

References

1 Clinicaltrials.gov. *A Global Multicenter Randomized Placebo-Controlled Phase 3 Trial To Compare The Efficacy And Safety Of Fruquintinib Plus Best Supportive Care To Placebo Plus Best Supportive Care In Patients With Refractory Metastatic Colorectal Cancer*. *Trial ID: NCT04322539*. 2020. Available from: https://clinicaltrials.gov/ct2/show/NCT04322539 [Accessed 1 December 2022].

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4 Zhang Y, Zou JY, Wang Z, Wang Y. Fruquintinib: a novel antivascular endothelial growth factor receptor tyrosine kinase inhibitor for the treatment of metastatic colorectal cancer. *Cancer Manag Res*. 2019;11:7787-803. Available from: https://doi.org/10.2147/cmar.S215533.

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