NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
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Tucatinib with trastuzumab for treating colorectal cancer

Company/Developer	Seagen Inc

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 33984	NICE ID: 11821	UKPS ID: 666657

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Tucatinib in combination with trastuzumab is in development for the treatment of adult patients with human epidermal growth factor receptor 2-positive (HER2+) metastatic colorectal cancer. Colorectal cancer is a type of cancer that starts in the end portions of the bowel in the digestive system, named the colon and the rectum. Metastatic cancer is cancer that has spread to other areas of the body than where it started meaning surgery is no longer a treatment option for these patients. The protein HER2 on cells promotes growth causing cancer to grow more effectively and can make the cancer harder to treat. There are currently no NICE recommended treatments for patients with HER2+ metastatic colorectal cancer.

Tucatinib is an oral twice-daily tyrosine kinase inhibitor of the HER2 protein which blocks cancer cell signalling and growth that is administered in combination with trastuzumab (intravenous administration once every 21 days). Trastuzumab is a monoclonal antibody that attaches to HER2 on cancer cells and prevents them from multiplying. If licensed, tucatinib in combination with trastuzumab will be the first treatment targeted for patients with HER2+ metastatic colorectal cancer.

Proposed Indication

Treatment of adult patients with human epidermal growth factor receptor 2-positive (HER2+) colorectal cancer.[1]

Technology

Description

Tucatinib (Tukysa) is an oral tyrosine kinase inhibitor of the HER2 protein which contributes to cancer cell growth. Tucatinib inhibits the phosphorylation of HER2 and HER3, resulting in inhibition of downstream mitogen-activated protein kinase (MAPK) and protein kinase B (AKT) signalling and proliferation, and showed anti-tumour activity in HER2-expressing tumour cells.[2] Trastuzumab (Herceptin) is a recombinant humanised IgG1 monoclonal antibody that binds with high affinity and specificity to sub-domain IV, a region of HER2's extracellular domain. Binding of trastuzumab to HER2 inhibits signalling and prevents the proteolytic cleavage of its extracellular domain, an activation mechanism of HER2. As a result, trastuzumab has been shown, in both in vitro assays and in animals, to inhibit the proliferation of human tumour cells that overexpress HER2.[3]

In the phase II trial (NCT03043313), tucatinib 300mg will be administered twice daily orally in combination with trastuzumab intravenously at a loading dose of 8mg/kg followed by a maintenance dose of 6mg/kg every 21 days.[4]

Key Innovation

There are currently no NICE recommended treatments for HER2+ metastatic colorectal cancers.[5] HER2 amplification also acts as a mechanism of resistance to anti EGFR therapies. HER2+ colorectal cancers generally have a worse prognosis than HER2- due to anti-epidermal growth factor receptor (EGFR)-targeted therapies having low efficacy in this group, highlighting need for specific treatments in this group.[6] The combination of tucatinib and the anti-HER2 antibody trastuzumab has also been shown to increase anti-tumour activity in vitro and in vivo compared to either medicine alone.[2] If licensed, tucatinib in combination with trastuzumab will be the first targeted treatment available to adult patients with HER2+ metastatic colorectal cancer.

Regulatory & Development Status

Tucatinib currently has Marketing Authorisation in the EU/UK for the treatment of adult patients with HER2+ locally advanced or metastatic breast cancer who have received at least two prior anti-HER2 treatments (in combination with trastuzumab and capecitabine).[7]

The combination of tucatinib and trastuzumab is also in phase III/ II clinical development for:[8]

- Breast cancer
- Solid tumours
- Brain metastases

Tucatinib and trastuzumab have the following regulatory designations/ awards:

- A breakthrough therapy by the US FDA in combination with trastuzumab for the treatment of adults with previously treated HER2+ colorectal cancer in July 2022.[9]

Patient Group

Disease Area and Clinical Need

Colorectal cancer is type of bowel cancer which has started in the colon or rectum within the digestive system, these are often grouped together due to the similar features they share in disease and organ function. The colon and rectum make up the large intestine.[10] Metastatic cancer, also known as stage 4 cancer, is where the cancer has spread to other areas of the body.[11] HER2 is an oncogenic driver and a well-established target in gastrointestinal cancers and breast cancer. Oncogenic activation of HER2 commonly occurs through gene amplification, resulting in protein overexpression of cells and unregulated cell growth.[12] The three 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 causes of bowel cancer aren't 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.[13]

Bowel cancer is the 4th most common type of cancer in the UK, accounting for 11% of all new cancer cases and the 2nd most common cause of cancer death (2016-18).[14] The age standardised incidence rate of bowel cancer in England is 83.6 and 55.8 per 100,000 amongst males and females respectively.[15] 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.[16] In the UK (2016-18) there were 42,886 patients diagnosed with bowel cancer and approximately 16,800 deaths each year (2017-19).[14] The one-year age standardised survival for adults diagnosed with stage four colorectal cancer in England (2013-17) is 43.9%, whereas the five-year survival rate is 10.3%.[17]

Recommended Treatment Options

There are no NICE recommended treatments for HER2+ metastatic colorectal cancer. In the advanced stages of colorectal cancer, where surgery isn't possible, a cure is currently unlikely via chemotherapy, but symptoms can be controlled and the spread of the cancer slowed using various treatments.[18]

Clinical Trial Information

Trial	**MOUNTAINEER;** NCT03043313, 2020-000540-60; A Phase II, Open Label Study of Tucatinib Combined With Trastuzumab in Patients With HER2+ Metastatic Colorectal Cancer **Phase II –** Active, not recruiting **Study completion date:** April 2023 **Location(s):** USA and 4 EU countries
Trial Design	Randomised, parallel assignment, open label
Population	N=117; patients with metastatic and/or unresectable HER2+, RAS-wildtype colorectal cancer; progression of disease after the last systemic therapy, or intolerant of the last systemic therapy; aged 18 years and older
Intervention(s)	Cohorts A and B- tucatinib twice daily for 21 days via oral administration, trastuzumab via intravenous administration on day one of each 21-day cycle Cohort C- tucatinib monotherapy, oral twice daily
Comparator(s)	No comparator used

Outcome(s)	Primary outcome measure: • Confirmed objective response rate (cORR) per RECIST 1.1 per blinded independent central review (BICR) in pooled cohorts A+B [Time frame: Up to 8 months] See trial record for full list of other outcomes
Results (efficacy)	In patients with chemotherapy refractory HER2+ metastatic colorectal cancer, tucatinib in combination with trastuzumab was well tolerated with clinically meaningful antitumor activity including durable responses and a median overall survival of 2 years. In cohorts A+B, the confirmed overall response rate by blinded independent central review was 38.1% (95% CI, 27.7, 49.3). The median duration of response was 12.4 months (95% CI, 8.5, 20.5). The median progression free survival was 8.2 months (95% CI, 4.2, 10.3), and the median overall survival was 24.1 months (95% CI, 20.3, 36.7).[4]
Results (safety)	The most common adverse events (AEs) in cohorts A+B were diarrhoea (64.0%), fatigue (44.2%), nausea (34.9%), and infusion-related reaction (20.9%); the most common AE of grade ≥3 was hypertension (7.0%). AEs leading to tucatinib discontinuation in cohorts A+B occurred in 5.8% of patients and included alanine amino transferase increase (2.3%), COVID-19 pneumonia (1.2%), cholangitis (1.2%), and fatigue (1.2%). No deaths resulted from AEs.[4]

Estimated Cost

The hospital indicative price of a packet of 84 tucatinib tablets (150mg) is £5,636.84.[19] The hospital indicative price of a vial of 600mg/5ml trastuzumab solution for injection is £1222.20.[20]

Relevant Guidance

NICE Guidance

- 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.[21]
- Healthcare Improvement Scotland. SIGN 126. Diagnosis and management of colorectal cancer. 2016.[22]

Additional Information

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