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Newcastle University

Health Technology Briefing
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TAS-102 with bevacizumab for treating refractory metastatic colorectal cancer after 2 previous therapies

Company/Developer	Servier Laboratories Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 31261	NICE TSID: Not available	UKPS ID: 668481

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

TAS-102 in combination with bevacizumab is currently in clinical development for the third-line treatment of refractory metastatic colorectal cancer (mCRC). Colorectal cancer, also known as bowel cancer, is cancer that affects the large bowel (colon cancer) or the back passage (rectal cancer). Common symptoms of colorectal cancer include a change in bowel habits or bleeding from the back passage, weight loss, and anaemia. Although the exact cause of colorectal cancer is unknown, risk factors include smoking, alcohol consumption, family history of the disease, being overweight or obese, and being inactive. There is an outstanding need for treatments that extend survival and maintain quality of life for patients with mCRC.

TAS-102 is a fixed dose combination of the drugs trifluridine and tipiracil. It is administered orally as a tablet. It works by disrupting DNA function in the targeted cancer cells, therefore reducing the spread of cancer cells. Trifluridine is inactivated rapidly when it enters the body, therefore tipriacil hydrochloride is administered concurrently to increase the effectiveness of trifluridine. Bevacizumab works by limiting blood supply to tumours to inhibit their growth. If licensed, TAS-102 in combination with bevacizumab will offer an additional treatment option for patients with previously treated mCRC, who currently have few options.

Proposed Indication

Previously treated, refractory, metastatic colorectal cancer (mCRC).[1]

Technology

Description

TAS-102 (trifluridine/tipiracil, lonsurf) is a thymidine-based nucleoside analogue that interferes with DNA function to reduce cancer cell proliferation. However, trifluridine is inactivated rapidly by thymidine phosphorylase after oral administration. Tipiracil hydrochloride, a thymidine phosphorylase inhibitor, is administered concurrently to increase the bioavailability of trifluridine.[2] Bevacizumab (Alymsys) acts by selectively binding circulating vascular endothelial growth factor (VEGF), thereby inhibiting the binding of VEGF to its cell surface receptors. This inhibition leads to a reduction in microvascular growth of tumour blood vessels and thus limits the blood supply to tumour tissues.[3]

TAS-102 in combination with bevacizumab is currently in clinical development for patients with previously treated mCRC. In the phase III clinical trial (NCT04737187/2020-001976-14), patients received TAS-120 35mg/m^2 orally twice daily in each cycle, in addition to bevacizumab 5mg/kg intravenous (IV) every 2 weeks.[1,2]

Key Innovation

There remains a need for treatments that extend survival and maintain quality of life. TAS-102 and bevacizumab have different mechanisms of action to target cancer cells. Compared to TAS-102 alone, TAS-102 with bevacizumab showed a survival and disease control benefit among patients with mCRC.[4]

If licensed, TAS-102 in combination with bevacizumab will offer an additional treatment option for patients with previously treated mCRC.

Regulatory & Development Status

TAS-102 as a monotherapy currently has Marketing Authorisation in the UK for the treatment of: [5]

- mCRC
- Metastatic gastric cancer

Bevacizumab currently has Marketing Authorisation in the UK for the treatment of:[3]

- mCRC (in combination with fluoropyrimidine based chemotherapy)
- metastatic HER2+ breast cancer (in combination with paclitaxel, or capecitabine)
- metastatic non-small cell lung cancer (in addition to platinum-based chemotherapy, or with erlotinib)
- metastatic renal cell cancer (in combination with interferon alfa 2a)
- advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (in combination with carboplatin and paclitaxel, or carboplatin and gemcitabine, or topotecan, or pegylated liposomal doxorubicin)
- metastatic cervical cancer (in combination with paclitaxel and cisplatin or, alternatively, paclitaxel and topotecan)

TAS-102 with bevacizumab is not in clinical development for any other indications.[6]

Patient Group

Disease Area and Clinical Need

Colorectal cancer, also known as bowel cancer, is cancer that affects the large bowel (colon cancer) or

the back passage (rectal cancer).[7] Although the exact cause of colorectal cancer is unknown, risk factors include smoking, alcohol consumption, family history of the disease, being overweight or obese and being inactive.[8] Common symptoms of colorectal cancer include a change in bowel habits or bleeding from the back passage, weight loss, and anaemia.[9] In some cases, the cancer causes a bowel obstruction and may lead to cramping pains in the abdomen, bloating, constipation and being unable to pass wind, or feeling nauseous.[10] Metastatic cancer refers to cancer that has spread from its place of origin to other parts of the body.[11]

Colorectal cancer is the fourth most common cancer in the UK, accounting for 11% of all new cancer cases and equates to around 42,900 new colorectal cancer cases in the UK annually (2016-2018). Colorectal cancer is more common in the White population than in other ethnic groups.[12] From 2017 to 2019, there were approximately 16,808 deaths annually attributable to colorectal cancer in the UK.[13] Mortality rates for colorectal cancer are highest in people aged over 90 years.[13] In England, 2021-22, there were 178,203 finished consultant episodes (FCE) and 162,089 admissions for malignant neoplasm of the colon, rectosigmoid junction, and rectum (ICD-10 code C18-20) which resulted in 331,176 FCE bed days and 125,188 day cases.[14]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) currently recommends the following therapies for previously treated mCRC:[15]

- regorafenib
- TAS-102 (trifluridine/tipiracil)

Clinical Trial Information

Trial	**SUNLIGHT;** NCT04737187, **EudraCT** 2020-001976-14; An Open label, Randomized, Phase III Study Comparing Trifluridine/Tipiracil in Combination with Bevacizumab to Trifluridine/Tipiracil Monotherapy in Patients with Refractory Metastatic Colorectal Cancer (SUNLIGHT Study) **Phase III** – Active, not recruiting **Location(s):** 9 EU countries, USA, and other countries **Primary completion date:** July 2022
Trial Design	Randomised, parallel assignment, open label
Population	N=490; adult patients aged ≥18 years old; histologically confirmed advanced unresectable adenocarcinoma of the colon or rectum, previously treated with a maximum of two prior chemotherapy regimens
Intervention(s)	TAS-102 35mg/m^2 twice daily in each cycle via oral administration; bevacizumab 5mg/kg every 2 weeks via intravenous administration.[1,2]
Comparator(s)	TAS-102 via oral administration
Outcome(s)	Primary outcome measure: - Overall Survival (OS) [Time Frame: Approximately 12 months] See trial record for full list of other outcomes
Results (efficacy)	Median OS was 10.8 months in the treatment arm and 7.5 months in the control arm; at 6 months, the OS rate was 77% vs 61%, respectively, and at 12 months,

	the OS rate was 43% vs 30%, respectively.[4]
Results (safety)	Zero reported treatment-related deaths. Rates of severe adverse effects (AEs) were 72% in the treatment arm and 70% in the control arm, and 13% of patients in both arms experienced AEs leading to withdrawal from the study.[4]

Estimated Cost

TAS-102 is already licensed in the UK. The NHS indicative price of TAS-102 (15mg/6.4ml) is £500 for 20 tablets and for TAS-102 (20mg/8.19mg),£666.67 for 20 tablets.[16]

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Regorafenib for previously treated metastatic colorectal cancer (TA866). February 2023.
- NICE technology appraisal. Trifluridine–tipiracil for previously treated metastatic colorectal cancer (TA405). August 2016.

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: Radiotherapy (All ages). B01/S/a.

Other Guidance

- European Society for Medical Oncology. Metastatic colorectal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment, and follow-up. 2023.[17]
- Scottish Intercollegiate Guidelines Network. Diagnosis and management of colorectal cancer (SIGN 126). 2016.[18]

Additional Information

References

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