

**NIHR Innovation Observatory
Evidence Briefing: July 2018****Trifluridine and tipiracil for metastatic gastric
cancer – third line and above**

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LAY SUMMARY

Gastric cancer is cancer that starts anywhere inside the stomach or the stomach wall. Advanced gastric cancer can be locally advanced (has spread into the tissues around the stomach) or metastatic (has spread to at least one other part of the body such as the liver). Most gastric cancer cases are diagnosed at a late stage and in people aged 75 years and over. Advanced cancers have poor prognosis and usually cannot be cured. However, they may be controlled, and symptoms can be relieved through treatment.

Trifluridine in combination with tipiracil in a single oral tablet, is in development for the treatment of metastatic gastric cancer, in patients who are refractory (resistant) to two prior standard treatments for the advanced disease. Trifluridine is incorporated into the DNA where it prevents cells from dividing and multiplying. The addition of tipiracil helps increase the level of trifluridine in the blood by slowing its breakdown. If licensed, trifluridine in combination with tipiracil will be an additional treatment option for patients with gastric cancer who have failed two prior therapies, who currently have very few treatment options available.

This briefing reflects the evidence available at the time of writing. A version of the briefing was sent to the company for a factual accuracy check. The company was available to provide comment. 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.

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TARGET GROUP

Metastatic gastric cancer (including adenocarcinoma of the gastroesophageal junction) – third line or later

TECHNOLOGY

DESCRIPTION

Trifluridine and tipiracil combination therapy (TAS-102; Lonsurf) comprises an antineoplastic thymidine-based nucleoside analogue, trifluridine, and the thymidine phosphorylase (TPase) inhibitor, tipiracil hydrochloride, at a molar ratio 1:0.5 (weight ratio, 1:0.471). Following uptake into cancer cells, trifluridine is phosphorylated by thymidine kinase, further metabolised in cells to a deoxyribonucleic acid DNA substrate, and incorporated directly into DNA, thereby interfering with DNA function to prevent cell proliferation. However, trifluridine is rapidly degraded by TPase and readily metabolised by a first-pass effect following oral administration, hence the inclusion of the TPase inhibitor, tipiracil hydrochloride.¹

Trifluridine and tipiracil combination therapy is in development for the treatment of metastatic gastric cancer in patients who are refractory to two prior standard treatments for advanced disease. In the phase III clinical trial (NCT02500043), patients received 35 mg/m²/dose of trifluridine and tipiracil orally, twice daily on days 1-5 and days 8-12 of each 28-day cycle as long as a benefit is observed or until unacceptable toxicity occurs.²

Trifluridine and tipiracil combination therapy is licensed in the EU for the treatment of adult patients with metastatic colorectal cancer who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents.¹

Common adverse events associated with trifluridine and tipiracil combination are: neutropenia, leukopenia, anaemia, thrombocytopenia, decreased appetite, diarrhoea, nausea, vomiting and fatigue.¹

INNOVATION and/or ADVANTAGES

Patients with metastatic gastric cancer have very limited treatment options available once their condition has become refractory to first and second line treatment.³ If licensed, trifluridine and tipiracil combination therapy could be an effective oral and potentially more convenient treatment option for patients with metastatic gastric cancer for whom two standard treatments have previously failed.

DEVELOPER

Servier Laboratories Ltd and Taiho Oncology Inc.

PATIENT GROUP

BACKGROUND

Stomach cancer is a malignant tumour originating in the cells of the stomach. The most common type of stomach cancer is gastric or gastro-oesophageal junction adenocarcinoma. Gastric cancer can start anywhere inside the stomach or within the stomach wall.⁴ Most gastric cancers originate in the gland cells in the inner stomach lining.⁵ Advanced gastric cancer is cancer that began in the stomach and has spread into the tissues around the stomach, either as locally advanced disease, or it can metastasise to other areas of the body such as the liver, lungs, lymph nodes, or the oesophagus. Advanced cancer cannot usually be cured, but treatment may control further growth of the disease, relieve symptoms and give the patient a good quality of life.⁶

Gastric cancer begins with a mutation in the structure of the DNA in cells, which can affect how they grow. This means cells grow and reproduce uncontrollably, resulting in a tumour. It is not known what triggers the changes in DNA that lead to gastric cancer. Some factors increase the risk of gastric cancer such as aging (55 years and older), male gender, smoking, severe chronic atrophic gastritis, peptic ulcers caused by *Helicobacter pylori* infection, diet such as pickled vegetables, salt and smoked meat, family history of gastric cancer, having another type of cancer, vitamin B12 deficiency, and history of stomach surgery.⁸

Common symptoms of gastric cancer include blood in stools or black stools, loss of appetite, weight loss, sickness, tiredness, breathlessness, lumpiness and swelling in the stomach (caused by a build-up of fluid), abdominal pain, dyspepsia and burping, anaemia, and jaundice.^{7,8}

Late complications of gastric cancer may include pathologic peritoneal and pleural effusions, obstruction of the gastric outlet or gastroesophageal junction, obstruction of the small bowel, bleeding in the stomach from oesophageal varices or the anastomosis after surgery, jaundice caused by hepatomegaly and weakness and weight loss from reduced appetite.⁹ The prognosis of patients with unresectable or metastatic gastric cancer is poor and the median survival time ranges between 6 and 12 months.¹⁰

CLINICAL NEED and BURDEN OF DISEASE

In 2015, gastric cancer was the 17th most common cancer in the UK. There were around 6,900 new cases of stomach cancer in the UK in 2013-2015, equivalent to 19 cases diagnosed every day.¹¹ The age-standardised incidence rate in England for malignant neoplasm of the stomach, in 2015, was 15.4 per 100,000 in males and 6.4 per 100,000 in females.¹² Between 2013 and 2015 around half (51%) of stomach cancer cases in the UK each year were diagnosed in people aged 75 years and over.¹¹

The proportion of gastric cancer cases in England diagnosed at stage III and stage IV in 2014 were 17% and 34% respectively. According to 2010-2012 data in the UK, the largest proportion of gastric cancer cases (34.0% males, 19.7% females) occur in the cardia (next to the oesophagus).¹³ In England, cancers of the gastro-oesophageal junction account for 40% of all cancers arising in the upper gastro-intestinal tract.¹⁴

Hospital episode statistics for England 2016/17 show that there were 20,249 hospital admissions for malignant neoplasm of stomach (ICD 10: C16), with 25,605 finished consultant episodes (FCE) resulting in 62,477 FCE bed days.¹⁵

According to 2010-2011 data, 19% of people diagnosed with stomach cancer in England and Wales survive their disease for five years or more.¹¹ Five year survival rates for stage III (A, B, C) gastric cancer were 25%, 20%, and 10% respectively; whereas those for stage IV was 5%.¹⁶

Gastric cancer was the 12th most common cause of cancer death in the UK in 2014. Crude mortality rate in England was 6.7 per 100,000 in 2014. In the UK, it is the eighth most common cause of cancer death in males, whilst it is the 13th most common cause of cancer death in females. Gastric cancer mortality is strongly related to age, with the highest mortality rates being in older males and females. In the UK in 2012-2014, on average each year around 6 in 10 (59%) deaths were in people aged 75 and over.¹⁷

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Pembrolizumab for gastric or gastroesophageal junction adenocarcinoma (ID1305). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Nivolumab for previously treated gastric or gastro-oesophageal junction cancer (ID1118). Expected date of issue to be confirmed
- NICE technology appraisal in development. Nivolumab in combination for previously untreated advanced gastric cancer (ID1465). Expected date of issue to be confirmed
- NICE technology appraisal in development. Avelumab for treating gastric or gastro-oesophageal junction cancer after 2 therapies (ID1289). Expected date of issue to be confirmed
- NICE technology appraisal in development. Pertuzumab for untreated metastatic HER2-positive gastric or gastro-oesophageal junction cancer (ID1096). Expected date of issue to be confirmed.
- NICE technology appraisal. Ramucirumab for treating advanced gastric cancer or gastro-oesophageal junction adenocarcinoma previously treated with chemotherapy (TA378). January 2016.
- NICE technology appraisal. Trastuzumab for the treatment of HER2-positive metastatic gastric cancer (TA208). November 2010.
- NICE technology appraisal. Capecitabine for the treatment of advanced gastric cancer (TA191). July 2010.
- NICE guideline in development. Oesophago-gastric cancer: assessment and management in adults (NG83). January 2018.
- NICE quality standard in development. Oesophago-gastric cancer (GID-QS10062). Expected December 2018.
- NICE interventional procedure guidance. Endoscopic submucosal dissection of gastric lesions (IPG360). October 2010.
- NICE interventional procedure guidance. Laparoscopic gastrectomy for cancer (IPG269). July 2008.
- NICE interventional procedure guidance. Laparo-endogastric surgery (IPG25). December 2003.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Oesophageal and gastric (Adult). B11/S/a.
- 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.
- NHS England. Clinical Commissioning Policy: Robotic assisted surgery for oesophago-gastric cancers. 16006/P. July 2016

OTHER GUIDANCE

- Gastric Cancer, Version 3. 2016, NCCN Clinical Practice Guidelines in Oncology. Journal of the National Comprehensive Cancer Network. 2016; 14:1286-1312.¹⁸
- Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 27 (Supplement 5): v38–v49, 2016.¹⁹
- LCA Oesophageal and Gastric Cancer Clinical Guidelines. April 2014.²⁰
- Guidelines for the management of oesophageal and gastric cancer. Gut 2011; 60: 1449e1472.²¹

CURRENT TREATMENT OPTIONS

The most common treatments for advanced gastric cancers are surgery, radiotherapy, and chemotherapy. The patient may have one of these treatments or a combination. If surgery is recommended, the patient may have radiotherapy or chemotherapy beforehand and after surgery. If it is not possible to remove the tumour completely, then the treatment focus will be on preventing the tumour from getting any bigger and causing further harm to the body. This can be done by surgery (palliative surgery) or by chemotherapy. When it is not possible to eliminate the cancer or slow it down, the aim of treatment will be to relieve the symptoms by surgery or radiotherapy.^{8, 22}

Trastuzumab in combination with cisplatin and capecitabine or 5-fluorouracil, is recommended as an option for the treatment of people with human epidermal growth factor receptor 2 (HER2)-positive metastatic adenocarcinoma of the stomach or gastro-oesophageal junction who have not received prior treatment for their metastatic disease and have tumours expressing high levels of HER2 as defined by a positive immunohistochemistry score of 3 (IHC3 positive).²³

For the second line treatment of metastatic oesophago-gastric cancer, palliative care is recommended, whilst the consideration of a suitable clinical trial as an alternative.²⁴ Patients with metastatic gastric cancer have very limited treatment options available once their condition has become refractory to first and second line treatment.³

Currently NICE has no recommendations for third line treatment of gastric cancer.

EFFICACY and SAFETY

Trial	NCT02500043 , EudraCT 2015-002683-16; TAS-102 vs placebo; phase III
Sponsor	Taiho Oncology, Inc
Status	Completed
Source of Information	Trial registry, ^{2,25} Presentation ²⁶
Location	EU (incl UK), USA, Canada and other countries
Design	Randomised, double-blind, placebo-controlled study
Participants	n=506; aged ≥18 years; histologically confirmed non-resectable, metastatic gastric adenocarcinoma including adenocarcinoma of the gastroesophageal junction; previously received at least 2 prior regimens for advanced disease and were refractory to or unable to tolerate their last prior therapy.
Schedule	Randomised to receive either: <ul style="list-style-type: none"> • 35 mg/m²/dose of TAS-102 orally, twice daily on days 1-5 and days 8-12 of each 28-day cycle with best supportive care. Continue for 4 cycles or until discontinuation criteria is met. • 35 mg/m²/dose of placebo orally, twice daily on days 1-5 and days 8-12 of each 28-day cycle with best supportive care. Continue for 4 cycles or until discontinuation criteria is met.
Follow-up	Active treatment for 4 (28 day) cycles or until discontinuation criteria was met. Patients who receive open-label TAS-102 treatment after conclusion of survival follow-up were followed for safety and tumour response according to the site standard of care. The end of study is defined as completion of safety follow-up for the last patient who discontinues study treatment, including patients who receive open-label TAS-102.
Primary Outcomes	Overall survival (OS) [Time Frame: Up to 3 years]
Secondary Outcomes	Progression-free survival (PFS) [Time Frame: Up to 3 years] Safety and tolerability [Time Frame: Up to 3 years]
Key Results	TAS-102 showed a clinically meaningful and statistically significant improvement in OS and PFS compared with placebo in a population of heavily pre-treated patients with metastatic gastric cancer. There were also: <ul style="list-style-type: none"> • 31% reduction in risk of death (HR, 0.69; 95% CI, 0.56–0.85; P=0.0003) • 2.1-month improvement in median OS (5.7 vs 3.6 months)
Adverse effects (AEs)	Grade ≥3 AEs were observed in 79% of patients who received TAS-102 and 58% who received placebo. The most frequently reported non-hematologic AEs were nausea, decreased appetite and fatigue. The most common grade 3/4 hematologic laboratory abnormalities were neutropenia and leukopenia. Grade ≥3 febrile neutropenia was reported in 6 patients (2%) treated TAS-102.
Expected reporting date	-

ESTIMATED COST and IMPACT

COST

The cost of trifluridine and tipiracil combination (Lonsurf) as 20 x 15mg/6.14mg tablets is £500.00.²⁷

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

- | | |
|--|--|
| <input checked="" type="checkbox"/> Reduced mortality/increased length of survival | <input checked="" type="checkbox"/> Reduced symptoms or disability |
| <input type="checkbox"/> Other | <input type="checkbox"/> No impact identified |

IMPACT ON HEALTH and SOCIAL CARE SERVICES

- | | |
|---|---|
| <input type="checkbox"/> Increased use of existing services | <input type="checkbox"/> Decreased use of existing services |
| <input type="checkbox"/> Re-organisation of existing services | <input type="checkbox"/> Need for new services |
| <input type="checkbox"/> Other | <input checked="" type="checkbox"/> None identified |

IMPACT ON COSTS and OTHER RESOURCE USE

- | | |
|--|---|
| <input checked="" type="checkbox"/> Increased drug treatment costs | <input type="checkbox"/> Reduced drug treatment costs |
| <input type="checkbox"/> Other increase in costs | <input type="checkbox"/> Other reduction in costs |
| <input type="checkbox"/> Other | <input type="checkbox"/> None identified |

OTHER ISSUES

- | | |
|---|---|
| <input type="checkbox"/> Clinical uncertainty or other research question identified | <input checked="" type="checkbox"/> None identified |
|---|---|

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