Lonsurf (trifluridine and tipiracil hydrochloride) for metastatic colorectal cancer – third line

SUMMARY

NIHR HSC ID: 10559

Lonsurf (trifluridine and tipiracil hydrochloride) is intended to be used as a third line therapy for the treatment of metastatic colorectal cancer previously treated with, or not considered suitable for current available therapies, including fluoropyrimidine, oxaliplatin, and irinotecan based chemotherapy, anti-VEGF therapy, and/or anti-EGFR therapy. If licensed, Lonsurf will offer an additional oral treatment option for such patients. Lonsurf does not currently have Marketing Authorisation in the EU for any indication.

Colorectal or bowel cancer is the fourth most common cancer in the UK. In England there were 34,044 cases of bowel cancer in 2011. The vast majority of people diagnosed with colorectal cancer are over 60 years of age. Between 20% and 55% of people presenting with colorectal cancer have metastatic disease, and an estimated 50-60% of patients who have undergone surgery for early stage colorectal cancer with apparently complete excision will eventually develop advanced disease and distant metastases. In England and Wales 13,879 deaths from colorectal cancer were registered during 2012.

The majority of patients with colorectal cancer have metastatic disease that initially is not suitable for potentially curative resection; therefore the aim of treatment is to convert initially unresectable disease to resectable disease, or is palliative, to control symptoms, extend survival and improve quality of life. Treatment may include chemotherapy such as FOLFOX, XELOX, irinotecan, FOLFIRI, or raltitrexed. Biological agents (alone or in combination with chemotherapy) such as cetuximab, bevacizumab, and panitumamb are an option for certain patients. Lonsurf is currently in two phase III clinical trials comparing its effect on overall survival against treatment with placebo. These trials are expected to complete between November 2014 and June 2016.
TARGET GROUP

- Colorectal cancer: metastatic – third line; previously treated with, or not considered suitable for current available therapies, including fluoropyrimidine, oxaliplatin, and irinotecan based chemotherapy, anti-VEGF therapy, and/or anti-EGFR therapy.

TECHNOLOGY

DESCRIPTION

Lonsurf (trifluridine and tipiracil hydrochloride, T15, T20; TAS 102) is an oral combination of trifluridine and tipiracil hydrochloride. Trifluridine is the active antitumour component of Lonsurf that inhibits thymidylate synthase. Its triphosphate form is incorporated into DNA in tumour cells following phosphorylation where it exerts an antitumor effect. Tipiracil hydrochloride inhibits degradation of trifluridine by inhibiting thymidine phosphorylase.

Lonsurf is administered orally at 35mg/m² twice daily for five days a week for 2 weeks, followed by a 14-day rest period. This treatment cycle is repeated every four weeks. Lonsurf does not currently have Marketing Authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

If licensed, Lonsurf will offer an additional oral treatment option for patients with metastatic colorectal cancer previously treated with, or not considered suitable candidates for current available therapies, a group who currently have few effective therapies available.

DEVELOPER

Taiho Pharma Europe Ltd.

AVAILABILITY, LAUNCH OR MARKETING

Lonsurf is currently in phase III clinical trials.

PATIENT GROUP

BACKGROUND

Colorectal cancer is a malignant tumour arising from the lining of the large intestine (colon and rectum)¹; almost two-thirds (66%) of all bowel cancers arise from the colon and over one-third (34%) arise from the rectum (including the anus)². There are a number of different histological types of colorectal cancer³:
- Adenocarcinoma – more than 95% of diagnosed colorectal cancers are adenocarcinomas. In addition, two rare adenocarcinomas of the colon and rectum, mucinous tumours and signet ring tumours, account for 1-2% of cases.
- Squamous cell carcinoma.
- Carcinoid tumour.
- Sarcoma.
- Lymphoma (approximately 1% of cases).
Symptoms of colorectal cancer may include: bleeding from the rectum or blood in the stools, a change in normal bowel habits (e.g. diarrhoea or looser stools lasting longer than four to six weeks), a lump in the rectum or abdomen, a feeling of needing to strain to pass a bowel motion, weight loss, pain in the abdomen or rectum, and anaemia. Sometimes a tumour may obstruct the bowel, which can result in symptoms including abdominal pain, feeling bloated, constipation, and vomiting\(^4,5\).

The cause of colorectal cancer in most people remains unknown, although factors such as age (over 65 years), obesity, smoking and high alcohol intake are believed to increase risk\(^6,7\). A diet high in fibre and low in saturated fat may reduce risk, whilst a diet high in red or processed meats may increase risk\(^6,7\). Family history and inherited conditions or related bowel conditions may greatly increase an individual’s risk of colorectal cancer\(^6,7\).

**NHS or GOVERNMENT PRIORITY AREA**

This topic is relevant to:

**CLINICAL NEED and BURDEN OF DISEASE**

Colorectal or bowel cancer is the fourth most common cancer in the UK, accounting for 13% of all new cases in 2011\(^2\). In England there were 34,044 cases of bowel cancer in 2011 (representing 46 cases per 100,000 population) (ICD-10 C18-C20)\(^3\). The occurrence of colorectal cancer is strongly related to age, with 86% of cases arising in people over 60 years of age\(^8\). In metastatic colorectal cancer the tumour has spread beyond the confines of the bowel and locoregional lymph nodes to other parts of the body\(^1\). Between 20% and 55% of people presenting with colorectal cancer have metastatic disease, and an estimated 50-60% of patients who have undergone surgery for early stage colorectal cancer with apparently complete excision will eventually develop advanced disease and distant metastases (typically presenting within 2 years of initial diagnosis)\(^1\).

The 5-year survival rate for metastatic colorectal disease is 6.6%\(^1\). In 2013-14 there were 137,937 admissions for colorectal cancer (ICD-10 C18-C20) in England, resulting in 379,266 bed days and 153,062 finished consultant episodes\(^10\). In England and Wales 13,879 deaths from colorectal cancer were registered during 2012\(^11\). The population likely to be eligible to receive Lonsurf could not be estimated from available published sources.

**PATIENT PATHWAY**

**RELEVANT GUIDANCE**

**NICE Guidance**
• NICE technology appraisal. Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer (TA212). December 2010.

**Other Guidance**

• European Society for Medical Oncology. Advanced Colorectal Cancer: ESMO Clinical Practice Guidelines. 2014.
• European Society for Medical Oncology. Rectal Cancer: ESMO Clinical Practice Guidelines. 2013.
• European Society for Medical Oncology. Familial Risk-Colorectal Cancer. ESMO Clinical Practice Guidelines. 2013.
• Scottish Intercollegiate Guidelines Network. Diagnosis and management of colorectal cancer. 2011.

**CURRENT TREATMENT OPTIONS**

The management of metastatic colorectal cancer is largely palliative, combining specialist treatments (palliative surgery, chemotherapy and radiation) with control of symptoms and psychosocial support. However, approximately 8% of people with metastatic colorectal cancer have potentially resectable liver metastases, and in some, chemotherapy may make these liver metastases operable. The majority of patients have metastatic disease that initially is not suitable for potentially curative resection; therefore the aim of treatment is to convert initially unresectable disease to resectable disease: and where this is not possible to control symptoms, extend survival and improve quality of life.

Treatment may include, as first or second line treatment:

**Chemotherapy**

• FOLFOX (folinic acid, 5-fluorouracil and oxaliplatin) as first or second line treatment.
• XELOX (capecitabine and oxaliplatin) as first line or second line treatment.
• Irinotecan as second line treatment.
• FOLFIRI (folinic acid, 5-fluorouracil and irinotecan) as first or second line treatment.
• Raltitrexed – only for patients who are intolerant to folinic acid, 5-fluorouracil, or for whom these drugs are not suitable.

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*Expert personal opinion.*
Biological agents
Current NICE guidance recommends cetuximab as a first line treatment – in combination with FOLFIRI or FOLFOX within its licensed indication for patients in whom19,21:

- The primary colorectal tumour has been resected or is potentially operable.
- The metastatic disease is confined to the liver and is unresectable.
- The patient is fit enough to undergo surgery to resect the primary colorectal tumour and to undergo liver surgery if the metastases become resectable after treatment. Expert opinion suggests that cetuximab is rarely used in the UK in this situation, as emerging research indicates that adding cetuximab may result in reduced survival post-operativelyb.

In England the remaining biological options for patients includeb:

- Bevacizumab as a second or third line treatment, in combination with an oxaliplatin containing regimen.
- Cetuximab as first-line treatment with either FOLFOX or an irinotecan containing regimen.
- Panitumab as a first line treatment, in combination with FOLFOX.
- Panitumumab (single agent) as a third or fourth line treatment.
- Cetuximab (single agent) as a third or fourth line treatment.

**EFFICACY and SAFETY**

<table>
<thead>
<tr>
<th>Trial</th>
<th>TERRA, NCT01955837; TAS-102 vs placebo; phase III.</th>
<th>RE COURSE, NCT01607957; TAS-102 vs placebo; phase III.</th>
<th>JPRN-JapicCTI-090880; TAS-102 vs placebo; phase II.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Taiho Pharmaceutical Co. Ltd.</td>
<td>Taiho Oncology Inc.</td>
<td>Taiho Pharmaceutical Co. Ltd.</td>
</tr>
<tr>
<td>Status</td>
<td>Ongoing</td>
<td>Published in abstract.</td>
<td>Published</td>
</tr>
<tr>
<td>Location</td>
<td>China, Republic of Korea, and Thailand.</td>
<td>EU (incl UK) USA, Australia and Japan.</td>
<td>Japan.</td>
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<tr>
<td>Participants</td>
<td>n=400 (planned); aged ≥18 years; adenocarcinoma of the colon or rectum; failed ≥2 prior regimens of standard chemotherapies for metastatic colorectal cancer; ECOG performance status of 0 or 1; able to take medication orally; adequate organ function (bone marrow, kidney and liver).</td>
<td>n=800; aged ≥18 years; adenocarcinoma of the colon or rectum; failed ≥2 prior regimens of standard chemotherapies for metastatic colorectal cancer; ECOG performance status of 0 or 1; able to take medication orally; adequate organ function (bone marrow, kidney and liver).</td>
<td>n=169; aged ≥20 years; colorectal cancer; failed ≥2 prior regimens of standard chemotherapies containing fluoropyrimidine, oxaliplatin, or irinotecan; ECOG performance status of 0 or 2; able to take medication orally; adequate organ function (bone marrow, kidney and liver).</td>
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<tr>
<td>Schedule</td>
<td>Randomised to TAS-102 35mg/m² orally, twice daily on days 1-5 and 8-12 of each 28-day cycle; or placebo orally, twice daily on days 1-5 and 8-12 of</td>
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</tr>
</tbody>
</table>

b Expert personal opinion.
Follow-up | Not reported. | As of the cut-off date of 31 Jan 2014, the average number of weeks of exposure was 12.7 weeks in the TAS-102 group, with a median of 6.7 weeks. As of the cut-off date of 24 Jan 2014, the mean number of months of follow-up for OS was 11.8 months. | Active treatment until tumour progression, unacceptable toxic effects or withdrawal of consent. As of the cut-off date of 4 Feb 2011, the median number of months of follow-up for OS was 11.3 months.

Primary outcome/s | Overall survival (OS). OS. OS. | PFS; overall response rate (ORR); disease control rate; AEs. No quality of life measurement included in trial outcomes. | PFS; objective response; disease control; duration of response; time to treatment failure; AEs. No quality of life measurement included in trial outcomes.

Secondary outcome/s | Progression-free survival (PFS); adverse effects (AEs). No quality of life measurement included in trial outcomes. | For the TAS-102 and placebo groups respectively: OS, 7.1 months vs 5.3 months, (hazard ratio [HR] 0.68, 1-sided p<0.0001); PFS, 2.0 months vs 1.7 months (HR 0.48, 1-sided p<0.0001); ORR, 1.6% vs 0.4% (non-significant); disease control rate, 44.0% vs 16.3% (2-sided p<0.0001). | For the TAS-102 and placebo groups respectively: OS, 9.0 months vs 6.6 months (HR 0.56, p=0.0011); median PFS\(^c\), 2.0 months vs 1.0 months (HR 0.41, p<0.0001); disease control\(^b\), 43% vs 11% (p<0.0001); time to treatment failure\(^b\), 1.9 months vs 1.0 months (HR 0.4, p<0.0001).

Key results | - | - | -

Adverse effects (AEs) | Very common (>10%) grade 3-4 AEs for TAS-102 and placebo groups respectively: neutropenia, 34.9 vs 0%; leukopenia, 12.8% vs 0%; anaemia, 16.5% vs 2.6%. | Very common (>10%) grade 3-4 AEs for the TAS-102 and placebo groups respectively: neutropenia, 50% vs 0%; leucopenia, 28% vs 0%; anaemia, 17% vs 5%; lymphopenia, 10% vs 4%.

Expected reporting date | Study completion date reported as June 2016. | Study completion date Nov 2014. | Study completion date Aug 2011.

ESTIMATED COST and IMPACT

COST

The cost of Lonsurf is not yet known.

\(^c\) As assessed by the independent review committee.
# Impact - Speculative

## Impact on Patients and Carers
- Reduced mortality/increased length of survival
- Reduced symptoms or disability\(^d\)
- Other.
- No impact identified

## Impact on Health and Social Care Services
- Increased use of existing services
- Decreased use of existing services: oral treatment option.
- Re-organisation of existing services
- Need for new services
- Other
- None identified

## Impact on Costs and Other Resource Use
- Increased drug treatment costs: due to increased length of drug administration\(^d\).
- Reduced drug treatment costs
- Other increase in costs
- Other reduction in costs
- Other: uncertain unit cost compared to existing treatments.
- None identified

## Other Issues
- Clinical uncertainty or other research question identified
- None identified

## References

8. Cancer Research UK. Data Table: Cancer cases and rates by country in the UK 2011 [publications.cancerresearchuk.org/cancerstats/statsincidence/dtinccountries.html](http://publications.cancerresearchuk.org/cancerstats/statsincidence/dtinccountries.html)

\(^d\) Expert personal opinion.


26 Yoshino T, Mayer R, and Falcone A. Results of a multicenter, randomised, double-blind, phase III study of TAS-102 vs. placebo, with best supportive care (BSC), in patients with metastatic

