Summary

The evidence to support tegafur/gimeracil/oteracil plus cisplatin for this indication derives from one pivotal phase III multicentre, randomised, open-label study to compare overall survival (OS) for cisplatin plus tegafur/gimeracil/oteracil (CS) with cisplatin plus 5-fluorouracil iv (CF) in adult patients with advanced gastric cancer, previously untreated with chemotherapy (FLAGS study). It is important to note that the comparator used in the FLAGS study (CF) is not relevant for UK practice, where patients would normally receive EOX or ECX.

The median follow-up was 18.3 months (range 12.1-31.8 months). The final primary analysis of survival was conducted in the full analysis set, which consisted of all patients who were dosed with study drug (n=521 for CS; n=508 for CF) and included deaths up to 12 months after the last patient was randomly assigned. The median survival of patients in the CS arm was 8.6 months compared with 7.9 months for patients in the CF arm (log-rank P=0.2; hazard ratio (HR) 0.92; 95% confidence interval (CI): 0.80 to 1.05).

The study was designed and conducted as a superiority study. However, the investigators considered it appropriate to switch post-hoc, after completion of the study, the primary objective from superiority to non-inferiority as the final results of the trial did not show statistical and clinical evidence for the primary objective: superiority of Teysuno®+cisplatin over 5-FU+cisplatin.

The ORR was 29.1% (n=402) in the CS group and 31.9% (n=385) in the CF group. The PFS was 4.8 months in the CS group and 5.5 months in the CF group; this difference was not statistically significant. The median TTF in both arms was 3.8 months.

On the basis of this data, and the cost-minimisation analysis (which showed cost savings with this regimen), the Scottish Medicines Consortium accepted tegafur/gimeracil/oteracil for restricted use in patients who are unsuitable for an anthracycline, fluorouracil and platinum triplet first-line regimen, i.e. the patient population for which the CDF application is made for.
Tegafur, gimeracil, and oteracil (known as S1) for first-line palliative treatment of advanced gastric cancer

**Background**

Stomach cancer is the ninth most common cancer in males in the UK and fourteenth in females (2). Gastric cancer is often diagnosed at an advanced stage (4). Advanced gastric cancer is incurable and the aim of palliative chemotherapy is to increase survival, prevent symptomatic deterioration and improve quality of life (1). In UK practice, epirubicin/oxaliplatin/capecitabine (EOX) or epirubicin/cisplatin/capecitabine (ECX) are often used for treating advanced metastatic gastric cancer.

Tegafur/gimeracil/oteracil (Teysuno®) is formulated as a fixed combination capsule containing tegafur, which is a fluoropyrimidine prodrug of 5-fluorouracil and two enzyme inhibitors: gimeracil and oteracil. Gimeracil reversibly inhibits the catabolism and inactivation of 5-fluorouracil by dihydropyrimidine dehydrogenase, and oteracil inhibits phosphorylation of 5-fluorouracil to 5-fluoridine-5'-monophosphate, the main compound responsible for gastrointestinal toxicity.

Teysuno® (known in the literature as S1) is licensed in the UK in adult patients for the treatment of advanced gastric cancer when given in combination with cisplatin (3). Teysuno® is accepted for restricted use within NHS Scotland for its licensed indication in patients who are unsuitable for an anthracycline, fluorouracil and platinum triplet first-line regimen (1).

**Epidemiology**

The age standardised incidence rate for stomach cancer in the UK in 2008 was 8.6/100,000 population (2).

True dihydropyrimidine dehydrogenase (DPD) deficiency affects 5% of the population and partial deficiency affects 3–5% of the population (6). DPD deficiency leads to capecitabine toxicity and so it can be predicted that patients with this deficiency will not be able to take capecitabine and will be eligible for tegafur/gimeracil/oteracil instead. It is estimated that cardiac toxicity requiring intervention occurs in 0.9–3.3% of patients receiving epirubicin, and 3–9% of patients receiving capecitabine (7). Patients with cardiac toxicity, who are not eligible for epirubicin or capecitabine, would be eligible for tegafur/gimeracil/oteracil to treat advanced gastric cancer instead.

Taking the DPD deficiency and cardiac toxicity incidences into account, the number of patients with advanced gastric cancer who would be eligible for tegafur/gimeracil/oteracil plus cisplatin would be 1.89/100,000.

**Published data**

The evidence to support the marketing authorisation of tegafur/gimeracil/oteracil derives from one pivotal phase III multicentre, randomised, open-label study to compare overall survival (OS) for cisplatin plus tegafur/gimeracil/oteracil (CS) with cisplatin plus 5-fluorouracil iv (CF) in adult patients with advanced gastric cancer, previously untreated with chemotherapy (FLAGS study) (4). The comparator used in the FLAGS study (CF) is not relevant for UK practice, where patients would normally receive EOX or ECX.

Patients aged ≥18 years with histologically confirmed, unresectable, locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma with a performance status of 0 or 1 by the Eastern Cooperative Oncology Group criteria were eligible. A total of 1,053 patients were randomised, 527 in the CS arm and 526 in the CF arm.

Baseline characteristics were similar in both treatment arms and reflected the population of patients with advanced gastric cancer. The majority of patients were male (70.8%) and white (86.0%). The mean age was 59 years: range 18-85 years and 14.2% ≥ 70 years of age. The Eastern Cooperative Oncology Group (ECOG) performance status was 0 for 41.4% of patients and 1 for 58.6% of patients.

All these patients had histological confirmed adenocarcinoma: 83.1% of the stomach and 16.9% of gastro-oesophageal junction. The most frequent pathology was poorly differentiated adenocarcinoma in 38.8% of patients.

The primary endpoint was superiority in overall survival from CS compared with CF. Secondary outcomes were overall response rate (ORR), progression-free survival (PFS), time to treatment failure (TTF) and safety.

In the CS arm, tegafur/gimeracil/oteracil was administered orally at 25mg/m² twice daily for 21 days and cisplatin was administered intravenously at 75mg/m² over one to three hours every 28 days. In the CF arm, 5-fluorouracil was administered at 1000mg/m² per 24 hours as an infusion over five days and cisplatin was administered intravenously at 100mg/m² over one to three hours every 28 days. All patients received hydration and standard prophylactic medication to reduce adverse effects. Cisplatin was discontinued after 6 cycles in both arms and tegafur/gimeracil/oteracil or 5-fluorouracil were continued until progression of disease or unacceptable adverse effects. Doses were reduced based on predefined criteria.

The median follow-up was 18.3 months (range 12.1-31.8 months) (5). The final primary analysis of survival was conducted in the full analysis set, which consisted of all patients who were dosed with study drug (n=521 for CS; n=508 for CF) and included deaths up to 12 months after the last patient was randomly assigned.
Tegafur, gimeracil, and oteracil (known as S1) for first-line palliative treatment of advanced gastric cancer

The median survival of patients in the CS arm was 8.6 months compared with 7.9 months for patients in the CF arm (log-rank P=0.2; hazard ratio (HR) 0.92; 95% confidence interval (CI): 0.80 to 1.05).

The study was designed and conducted as a superiority study. However, the investigators considered it appropriate to switch post-hoc, after completion of the study, the primary objective from superiority to non-inferiority, discussing the criteria in accordance with the CHMP Points to Consider on Switching between Superiority and Non-inferiority, as the final results of the trial did not show statistical and clinical evidence for the primary objective: superiority of Teysuno®+cisplatin over 5-FU+cisplatin (5).

The ORR was 29.1% (n=402) in the CS group and 31.9% (n=385) in the CF group. The PFS was 4.8 months in the CS group and 5.5 months in the CF group; this difference was not statistically significant. The median TTF in both arms was 3.8 months.

Safety

The dose of cisplatin used in the CS arm (75mg/m²) was lower than that used in the CF group (100mg/m²), which may account for the different frequencies of some of the adverse events between the treatment groups. The percentage of patients who developed at least one treatment-related serious adverse event was lower with CS (20%) than with CF (30%) (p<0.05) and there were significantly fewer renal adverse events and electrolyte imbalances reported with CS compared with CF (1).

Oteracil is intended to reduce the gastro-intestinal adverse effects associated with 5-fluorouracil. In the FLAGS study, the overall incidence of diarrhoea (29% for CS versus 38% for CF; p<0.01) and the use of anti-diarrhoeal medication (30% for CS versus 49% for CF) were lower in the CS arm. However, the occurrence of grade 3-4 diarrhoea was not significantly different between the two treatment groups (4.8% for CS versus 4.5% for CF) (1).

Overall, the adverse events reported in the FLAGS study were consistent with the known safety profile of fluoropyrimidines and included anaemia (44% for CS versus 46.1% for CF), nausea (62% for CS versus 67% for CF), vomiting (48% for CS versus 55% for CF [p=0.05]), fatigue (39% for CS versus 39% for CF) and anorexia (32% for CS versus 34% for CF) (1) (8).

There were significantly fewer myelosuppression-related serious adverse events with the CS regimen compared with the CF regimen. Febrile neutropenia was reported in 1.9% of patients in the CS arm compared with 6.9% of patients in the CF arm (p<0.001). Grade 3–4 neutropenia occurred in 18.6% of patients treated with CS compared with 40% of patients treated with CF (p<0.001); grade 3–4 thrombocytopenia occurred in 5.4% of patients treated with CS compared with 8.5% of patients treated with CF (p=0.064) and grade 3–4 leucopenia occurred in 7.3% of patients treated with CS compared with 13.8% of patients treated with CF (p=0.001) (8).

There were significantly fewer treatment-related deaths with CS (n=13; 2.5%) than with CF (n=25; 4.9%) (p<0.05). There were 4 (0.8%) myelosuppression-related deaths in the CS group and 14 (2.8%) in the CF group (p<0.05) (1).

Hyperbilirubinaemia ≥grade 3 (6.5% for CS versus 3.6% for CF; p<0.05), palmar-plantar erythrodysaesthesia (5.4% for CS versus 2.6% for CF; p<0.05) and increased lacrimation (6.1% for CS versus 1.2% for CF; p<0.05) were all reported significantly more frequently in the CS arm (1).

Cost

The price of 15mg Teysuno® 126-capsule pack is £336 (including VAT). The price of 20mg Teysuno® 84-capsule pack is £298 (including VAT). Assuming BSA of 1.75m², a patient would take three 15mg capsules twice daily for 21 days in each cycle, which equates to one pack of 126 capsules per cycle. The cost per cycle per patient would be £336.

In the FLAGS study, tegafur/gimeracil/oteracil was continued until progression and PFS was reported as 4.8 months in this cohort, which would be approximately 5 cycles. The cost for one patient to be treated with Teysuno® for 5 cycles would be £1680 (including VAT).

The Scottish Medicines Consortium review included a cost-minimisation analysis of tegafur/gimeracil/oteracil plus cisplatin (CS) versus either cisplatin and 5-fluorouracil (CF), cisplatin and capecitabine 1000mg/m² (CX 1000mg), cisplatin and capecitabine 625mg/m² (CX 625mg), or oxaliplatin and capecitabine (OX) (1). Equivalence between CS and CX 1000mg/CX 625mg/OX was assumed based on indirect comparisons. Results were presented for time horizons of 12 weeks and 18 weeks and are shown below:
Tegafur, gimeracil, and oteracil (known as S1) for first-line palliative treatment of advanced gastric cancer

January 2013
London Cancer New Drugs Group

The median follow-up was 18.3 months (range 12.1-31.8 months). The final primary analysis of survival was conducted in the full analysis set, which consisted of all patients who were dosed with study drug (n=521 for CS; n=508 for CF) and included deaths up to 12 months after the last patient was randomly assigned. The median survival of patients in the CS arm was 8.6 months compared with 7.9 months for patients in the CF arm (log-rank P=0.2; hazard ratio (HR) 0.92; 95% confidence interval (CI): 0.80 to 1.05).

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<table>
<thead>
<tr>
<th>12 weeks (3 cycles of CS and 4 cycles of all other regimens)</th>
<th>CX 1000mg</th>
<th>CX 625mg</th>
<th>CF</th>
<th>CS</th>
<th>OX</th>
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</thead>
<tbody>
<tr>
<td>Drug administration</td>
<td>£1,477</td>
<td>£1477</td>
<td>£4791</td>
<td>£1108</td>
<td>£1477</td>
</tr>
<tr>
<td>Drug acquisition</td>
<td>£1,142</td>
<td>£1019</td>
<td>£346</td>
<td>£1008</td>
<td>£3539</td>
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<td>Total cost</td>
<td>£2619</td>
<td>£2496</td>
<td>£5137</td>
<td>£2116</td>
<td>£5016</td>
</tr>
<tr>
<td>Cost saving with CS</td>
<td>£503</td>
<td>£380</td>
<td>£3021</td>
<td>-</td>
<td>£2900</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>18 weeks (4.5 cycles of CS and 6 cycles of all other regimens)</th>
<th>CX 1000mg</th>
<th>CX 625mg</th>
<th>CF</th>
<th>CS</th>
<th>OX</th>
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</thead>
<tbody>
<tr>
<td>Drug administration</td>
<td>£2216</td>
<td>£2216</td>
<td>£7187</td>
<td>£1662</td>
<td>£2216</td>
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<tr>
<td>Drug acquisition</td>
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<td>£5308</td>
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<tr>
<td>Total cost</td>
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<td>£3745</td>
<td>£7706</td>
<td>£3174</td>
<td>£7524</td>
</tr>
<tr>
<td>Cost saving with CS</td>
<td>£755</td>
<td>£571</td>
<td>£4532</td>
<td>-</td>
<td>£4350</td>
</tr>
</tbody>
</table>

The Scottish Medicines Consortium considered that the economic case for CS had been demonstrated and that CS was the preferred treatment on cost-minimisation grounds.

Service implications
Tegafur/gimeracil/oteracil is an oral capsule and is administered with cisplatin (an IV infusion given on one day in 28 days). The current UK standard treatment is EOX or ECX, which involves intravenous doses of epirubicin with either cisplatin or oxaliplatin given on one day in 21 days, and also oral capecitabine. It would therefore be expected that there will be a reduction in the capacity burden on the outpatient cancer day unit due to the reduction in the intravenous doses administered.

Summary
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<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Incidence (number of patients per 100,000 eligible for this treatment)</th>
<th>Average duration of treatment (taken from trial data)</th>
<th>Cost per month/cycle</th>
<th>Cost per 100,000 population per month/cycle</th>
<th>Cost per 100,000 for average treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tegafur/gimeracil/oteracil</td>
<td>Advanced metastatic gastric cancer as an alternative to standard chemotherapy when standard treatment not possible due to capecitabine toxicity or cardiac toxicity</td>
<td>1.89/100,000</td>
<td>4.8 months (approximately 5 cycles)</td>
<td>£336 per cycle</td>
<td>£635 per cycle</td>
<td>£3175</td>
</tr>
</tbody>
</table>

References

Details of search strategy:

1. EMBASE; GIMERACIL PLUS OTERACIL POTASSIUM PLUS TEGAFUR/; 914 results.
2. EMBASE; STOMACH CANCER/; 37949 results.
3. EMBASE; 1 AND 2; 358 results.
4. EMBASE; *GIMERACIL PLUS OTERACIL POTASSIUM PLUS TEGAFUR/; 503 results.
5. EMBASE; 2 AND 4; 209 results.
6. MEDLINE; TEGAFUR/; 4187 results.
7. MEDLINE; STOMACH NEOPLASMS/; 68620 results.
8. MEDLINE; 6 AND 7; 1439 results.
9. MEDLINE; *TEGAFUR/; 1823 results.
10. MEDLINE; 7 AND 9; 625 results.
11. MEDLINE; *STOMACH NEOPLASMS/; 56472 results.
12. MEDLINE; 9 AND 11; 576 results.
13. MEDLINE; gimeracil.ti,ab; 79 results.
14. MEDLINE; oteracil.ti,ab; 63 results.
15. MEDLINE; 12 AND 13 AND 14; 9 results.
16. EMBASE; "Ajani JA".au; 498 results.
17. EMBASE; "Bodoky G".au; 84 results.
18. EMBASE; "Strumberg D".au; 116 results.
19. EMBASE; 16 AND 17; 4 results.
20. EMBASE; 16 AND 18; 3 results.
21. EMBASE; STOMACH TUMOR/; 37070 results.
22. EMBASE; TEGAFUR/; 5656 results.
23. EMBASE; 21 AND 22; 823 results.
24. EMBASE; *STOMACH TUMOR/; 29722 results.
25. EMBASE; CISPLATIN/; 112544 results.
26. EMBASE; 22 AND 24 AND 25; 316 results.
27. MEDLINE; TEGAFUR/; 4187 results.
28. MEDLINE; *STOMACH NEOPLASMS/; 56472 results.
29. MEDLINE; CISPLATIN/; 37391 results.
30. MEDLINE; 27 AND 28 AND 29; 500 results.
31. EMBASE; 26 [Limit to: Human and English Language]; 26 results.
32. MEDLINE; 30 [Limit to: English Language and Humans]; 151 results.
33. EMBASE, MEDLINE; Duplicate filtered: [26 [Limit to: Human and English Language]], [30 [Limit to: English Language and Humans]]; 177 results.

The document reflects the views of LCNDG and may not reflect those of the reviewers