Ramucirumab monotherapy for advanced gastric cancer and gastro-oesophageal junction adenocarcinoma – after prior chemotherapy.

SUMMARY

Ramucirumab is a fully human IgG1 monoclonal antibody, which acts as a vascular endothelial growth factor receptor-2 (VEGFR-2) antagonist. VEGFR-2 is present on endothelial cells in tumours and is responsible for tumour angiogenesis. Inhibition of VEGFR-2 may prevent the formation of new blood vessels and thereby limit nutrient supply to the tumour, causing death of tumour cells. Ramucirumab is administered by intravenous (IV) infusion at 8mg/kg every 2 weeks.

Around 7,800 people are diagnosed with stomach cancer in the UK each year. The most common type of stomach cancer is gastric or gastro-oesophageal junction adenocarcinoma which together accounts for 95% of all cases in the UK. Gastric cancer is the eighth most common cancer in males in the UK and the thirteenth in females. In England during 2010, there were 5,910 new cases of malignant neoplasm of the stomach (including oesophageal junction). The proportion of patients who have metastatic disease is estimated to be 80%, which is equal to 4,728 people. An estimated 1,654 patients per year receive first line chemotherapy for gastric adenocarcinoma. In England during 2011, there were 20,494 admissions recorded for malignant neoplasm of the stomach accounting for 79,633 bed days and 25,976 finished consultant episodes. In 2010, there were 4,199 deaths from malignant neoplasm of the stomach in England and Wales.

There is no standard second line treatment for patients with advanced gastric or gastro-oesophageal junction adenocarcinoma following progression despite prior chemotherapy. Ramucirumab in combination with best supportive care is currently undergoing a phase III clinical trial comparing its effect on overall survival with placebo.
TARGET GROUP

- Gastric cancer: locally advanced or metastatic – following disease progression with prior chemotherapy.
- Gastro-oesophageal junction adenocarcinoma: locally advanced or metastatic – following disease progression with prior chemotherapy.

TECHNOLOGY

DESCRIPTION

Ramucirumab (IMC-1121B; LY3009806) is a fully human IgG1 monoclonal antibody, which acts as a vascular endothelial growth factor receptor-2 (VEGFR-2) antagonist. Ramucirumab inhibits ligand stimulated activation of VEGFR-2 and its downstream signalling components. VEGFR-2 is present on endothelial cells in tumours and is responsible for tumour angiogenesis. Inhibition of VEGFR-2 may prevent the formation of new blood vessels and thereby limit nutrient supply to the tumour causing death of tumour cells. Ramucirumab is administered by intravenous (IV) infusion at 8mg/kg every 2 weeks.

Ramucirumab is also in phase III development for gastric cancer (in combination with paclitaxel), breast cancer, colorectal cancer, liver/hepatocellular cancer and non-small cell lung cancer. It is in phase II development for brain cancer, bladder cancer, ovarian cancer, prostate cancer and renal cancer.

INNOVATION and/or ADVANTAGES

If licensed, ramucirumab will offer an additional treatment option for patients with advanced disease whose disease has progressed despite prior fluropyrimidine and platinum chemotherapy, and for whom there are currently no standard therapies available.

DEVELOPER

Eli Lilly and Company Limited.

AVAILABILITY, LAUNCH OR MARKETING

Ramucirumab is a designated orphan drug in the EU and USA.

Ramucirumab is currently in phase III clinical trials.

PATIENT GROUP

BACKGROUND

Around 7,800 people are diagnosed with stomach cancer in the UK each year¹. There are several different types of stomach cancer. The most common type is gastric or gastro-oesophageal junction adenocarcinoma, which starts in the glandular cells of the stomach lining and accounts for 95% of stomach cancers in the UK. Other rarer types of cancer that can affect the stomach include:
• soft tissue sarcomas, of which the commonest are leiomyosarcomas and gastrointestinal stromal tumours (GISTs).
• lymphomas such as mucosa associated lymphoid tissue (MALT) lymphomas; and carcinoid tumours.

The initial symptoms of gastric cancer are often vague and may be mistaken for other conditions\(^2\). They may include\(^2,3\): uncomplicated dyspepsia, abdominal pain and feeling full or bloated after a small meal. More general symptoms may also be observed, such as decreased appetite, fatigue, weakness and weight loss. Symptoms of advanced gastric cancer may include\(^2,3\): an epigastric mass, hepatomegaly, jaundice, ascites, blood in the stool, vomiting, anorexia, Troiser’s sign (an enlarged supraclavicular node – Virchow’s node) and acanthosis nigricans.

Risk factors associated with gastric cancer and gastro-oesophageal junction adenocarcinoma may include\(^4\): age, gender (male), alcohol use, tobacco use, poor diet, \textit{Helicobacter pylori} infection, gastro-oesophageal reflux disease (GORD), oesophagitis, pernicious anaemia, and Barrett’s oesophagus (abnormality of the epithelial cells of the distal oesophagus).

**NHS or GOVERNMENT PRIORITY AREA**

This topic is relevant to: Improving Outcomes: A Strategy for Cancer (2011).

**CLINICAL NEED and BURDEN OF DISEASE**

Gastric cancer is the eighth most common cancer in males in the UK and the thirteenth in females\(^5\). In England during 2010, there were 5,910 new cases of malignant neoplasm of the stomach (including oesophageal junction) (ICD C16)\(^6\). Gastric cancer has greater incidence in older people\(^1\) and almost twice as many men than women are diagnosed with gastric tumours\(^7\). Less than 8% of cases are diagnosed before the age of 55 years and the rates increase steeply from age 60, reaching a rate of around 141 per 100,000 population in men aged 85 and over\(^1\). However, stomach cancer mortality rates in the UK have fallen by around 75% over the last 40 years\(^8\).

Cancers of the oesophagus and stomach are usually diagnosed at a late stage and therefore have a poor prognosis. The proportion of patients who have metastatic disease is estimated to be 80%\(^7\), which is equal to 4,728 people. Of patients with advanced disease, it is estimated that 66% have inoperable cancer, and of these 53% are estimated to be fit enough to receive first-line chemotherapy\(^5\). Therefore an estimate of patients with gastric adenocarcinoma who receive first line chemotherapy is 1,654 patients per year. In England during 2011, there were 20,494 admissions recorded for malignant neoplasm of the stomach (ICD C16) accounting for 79,633 bed days and 25,976 finished consultant episodes\(^10\). There were 4,199 deaths from malignant neoplasm of the stomach (ICD C16)\(^11\) in England and Wales during 2010.
PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance


Other Guidance

- European Society for Medical Oncology (ESMO). Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.

EXISTING COMPARATORS and TREATMENTS

There is currently no standard second line treatment for patients with advanced gastric or gastro-oesophageal junction adenocarcinoma following progression despite prior chemotherapy, although expert opinion suggests that most UK centres will use docetaxel and/or irinotecan chemotherapy in this patient group. Wherever possible it is recommended that patients are enrolled into a RCT. The goals of therapy are symptom control (e.g. relief of dysphagia), improving survival, and improving quality of life. Treatment options may include:

- Palliative pharmaceutical therapies
  - The following combination chemotherapy regimens have been used in trials:
    - Irinotecan in combination with cisplatin or fluoropyrimidines
    - Docetaxel monotherapy
    - Docetaxel in combination with oxaliplatin
    - Paclitaxel alone or in combination with platinum agents
    - FOLFOX (folinic acid, 5-FU, oxaliplatin)
- Palliative radiotherapy
- Endoscopic methods for relieving dysphagia
  - Oesophageal intubation
  - Oesophageal dilatation
  - Brachytherapy and stents
  - Iatrogenic perforation and tracheo-oesophageal fistulae
- Laser therapy and stents
- Palliative surgery – to bypass obstruction in patients with distal stomach cancers that are obstructing the passage of food out of the stomach.

a Expert clinical opinion.
## EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>REGARD, NCT00917384; ramucirumab vs placebo, both in combination with best supportive care; phase III.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>ImClone LLC.</td>
</tr>
<tr>
<td>Status</td>
<td>Complete and published in abstract.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Abstract, trial registry, manufacturer.</td>
</tr>
<tr>
<td>Location</td>
<td>EU (inc UK), USA, Canada and other countries.</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised, placebo-controlled.</td>
</tr>
<tr>
<td>Participants</td>
<td>n=355; aged ≥18 years; gastric carcinoma, including gastric adenocarcinoma or gastro-oesophageal junction adenocarcinoma; metastatic disease or locally recurrent, unresectable disease with measurable lymph node metastases; measurable and/or evaluable disease as defined by RECIST; disease progression ≤4 months after the last dose of first line therapy for metastatic disease, ≤6 months after the last dose of adjuvant therapy; life expectancy ≥12 weeks.</td>
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<tr>
<td>Schedule</td>
<td>Randomised to ramucirumab 8mg/kg IV every 2 weeks or placebo 8mg/kg IV every 2 weeks; both in combination with best supportive care (may include but not limited to antiemetic agents, opiate and non-opiate analgesics, appetite stimulants, and granulocyte and erythroid growth factors).</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Continuous active treatment.</td>
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<tr>
<td>Primary outcome/s</td>
<td>Overall survival (OS).</td>
</tr>
<tr>
<td>Secondary outcome/s</td>
<td>Progression free survival (PFS) at week 12; objective response rate (ORR); duration of response; EORTC-QLQ-C30; adverse events; antibodies against ramucirumab at week 12;</td>
</tr>
<tr>
<td>Key results</td>
<td>For ramucirumab vs placebo respectively: median OS, 5.2 months vs 3.8 months; all-cause mortality, reduced by 22% (hazard ratio [HR] 0.776, 95% CI 0.603-0.998, p=0.047); median PFS, 2.1 months vs 1.3 months (HR 0.483, 95% CI 0.376-0.620, p&lt;0.0001); disease control rate, 40% vs 23% (p=0.0001); use of further anti-cancer therapy post-study, 32% vs 39%.</td>
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<tr>
<td>Adverse effects (AEs)</td>
<td>The most frequent grade ≥3 AEs for ramucirumab and placebo respectively were: hypertension (7.6%, 2.6%), fatigue (6.4%, 9.6%), anaemia (6.4%, 7.8%), abdominal pain (5.9%, 2.6%), ascites (4.2%, 4.3%), decreased appetite (3.4%, 3.5%), bleeding (3.4%, 2.6%), and hyponatremia (3.4%, 0.9%).</td>
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</table>

## ESTIMATED COST and IMPACT

### COST

The cost of ramucirumab is not yet known.

### IMPACT - SPECULATIVE

<table>
<thead>
<tr>
<th>Impact on Patients and Carers</th>
<th>☑ Reduced mortality/increased length of survival</th>
<th>☑ Reduced symptoms or disability</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ Other:</td>
<td>☐ No impact identified</td>
<td></td>
</tr>
</tbody>
</table>

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b RECIST: Response Evaluation Criteria In Solid Tumours.

c The European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-Core 30: includes five functional scales, three symptom scales, global health status, and six single items.
### Impact on Services

- Increased use of existing services
- Decreased use of existing services
- Re-organisation of existing services
- Need for new services
- Other: None identified

### Impact on Costs

- Increased drug treatment costs
- Reduced drug treatment costs
- Other increase in costs:
- Other reduction in costs:
- Other: None identified

### Other Issues

- Clinical uncertainty or other research question identified: *expert clinical opinion suggests that most UK centres will use docetaxel and/or irinotecan chemotherapy in this patient group. Expert opinion also highlights that recent evidence in this setting indicates a benefit for docetaxel vs best supportive care and that further research evaluating ramucirumab use in the third line setting may be more appropriate*. None identified

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**REFERENCES**


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*d* Expert clinical opinion.
17 Fuchs CS, Tomasek J, Yong Cho J et al. REGARD: A phase III, randomized, double-blinded trial of ramucirumab and best supportive care (BSC) versus placebo and BSC in the treatment of metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma following disease progression on first-line platinum- and/or fluoropyrimidine-containing combination therapy. Journal of Clinical Oncology 30:2012 (supplement 34;abstract LBA5).