Pertuzumab for metastatic HER2-positive gastric cancer – first line

NIHR HSRIC ID: 7356

Lay summary

Pertuzumab is a new drug to treat stomach cancer. It is delivered straight into the blood via a drip. Pertuzumab may help the body’s immune system to fight the disease. Stomach cancer is an unusual type of cancer. Gastric and gastroesophageal junction adenocarcinoma are the most common types of stomach cancer. Pertuzumab may offer a new treatment option for people with stomach cancer that has one particular type of genetic mutation and whose disease has spread to other parts of the body.

This briefing is based on information available at the time of research and a limited literature search. 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.

This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.
TARGET GROUP

- Adenocarcinoma of the stomach or gastro-oesophageal junction: metastatic; HER2-positive – first line; in combination with cisplatin and trastuzumab and either 5-fluorouracil or capecitabine.

TECHNOLOGY

DESCRIPTION

Pertuzumab (Perjeta; 2C4 antibody; Omnitarg; R-1273; RG-1273; rhuMAb 2C4; RO-4368451) is a recombinant humanised monoclonal antibody that specifically targets the extracellular dimerisation domain (subdomain II) of the human epidermal growth factor receptor 2 (HER2) protein. It prevents the dimerisation of HER2 with other HER family receptors at the surface of cancer cells, which inhibits intracellular signalling pathways, leading to cell growth arrest and apoptosis. In addition, pertuzumab mediates antibody-dependent cell-mediated cytotoxicity. In the phase 3 trial, pertuzumab was administered via 840mg intravenous (IV) infusion every 3 weeks in combination with 5-fluorouracil (5FU) 800mg/m²/24 hours IV by continuous infusion for 120 hours (days 1-5) every 3 weeks or capecitabine 1,000mg/m² orally twice daily, evening of day 1 to morning of day 15 (28 doses) every 3 weeks; cisplatin 80mg/m² IV every 3 weeks; and trastuzumab 8mg/kg IV initial dose on day 1, followed by 6mg/kg IV every 3 weeks, for 6 cycles¹.

Pertuzumab is licensed in the EU for the first line treatment of HER2-positive metastatic or locally recurrent unresectable breast cancer when combined with trastuzumab and docetaxel. It is also licensed for the neoadjuvant treatment of HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence in combination with trastuzumab and chemotherapy.

The most common adverse effects (≥50%) seen with pertuzumab in combination with trastuzumab and docetaxel are: diarrhoea, alopecia, neutropenia and nausea². Other common (≥10%) adverse effects include: (febrile) neutropenia, leucopenia, upper respiratory tract infection, rashes, headache, fatigue, nasopharyngitis, asthenia, pruritus, arthralgia, pain in extremities, back pain and coughing.

Pertuzumab is in phase III clinical trials for the treatment of HER2-positive breast cancer as a combination therapy and ovarian cancer.

INNOVATION and/or ADVANTAGES

If licensed, pertuzumab will offer an additional treatment option for patients with HER2-positive metastatic gastric cancer.

DEVELOPER

Roche Products Ltd.

AVAILABILITY, LAUNCH OR MARKETING

Pertuzumab is currently in phase III clinical trials.
PATIENT GROUP

BACKGROUND

There are several different types of stomach cancer, the most common being gastric or gastroesophageal junction adenocarcinoma, which starts in the glandular cells of the stomach lining. Initial symptoms are often vague and are similar to the symptoms of other stomach conditions. Early symptoms include heartburn or indigestion, burping, no appetite and feeling full after eating only a small amount. Symptoms of advanced stomach cancer may include a lack of appetite and subsequent weight loss, fluid in the abdomen and blood in the stool. Risk factors include increasing age, being male, a family history, infection with Helicobacter pylori, a diet low in fruit and vegetables and high in processed meats or smoked foods, smoking, being overweight, and long-term acid reflux or stomach conditions that cause changes to the stomach lining.

CLINICAL NEED and BURDEN OF DISEASE

Gastric cancer is the 16th most common cancer in the UK, accounting for around 2% of all new cases. In England, there were 5,342 cases of malignant neoplasm of stomach (ICD-10 C16) recorded in 2014. Gastric cancer is more common in men, with approximately twice as many cases diagnosed in men as in women. Gastric or gastroesophageal junction adenocarcinoma are the most common types of stomach cancer and accounts for 95% of stomach cancers in the UK. Due to the nature of symptoms, stomach cancer is often diagnosed at an advanced stage, with around 14% diagnosed at stage 3 (locally advanced), and 80% diagnosed at stage 4 (metastatic). It is estimated that 22% of patients with advanced gastric cancer have HER2-positive disease.

Survival is poor, with around 75% of cases presenting with disease too established for curative treatment. In 2014-15, there were 19,534 hospital admissions for malignant neoplasm of stomach, resulting in 68,097 bed days and 24,849 finished consultant episodes. In 2014, there were 3,949 deaths from malignant neoplasm of stomach in England and Wales.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance

CURRENT TREATMENT OPTIONS

The aim of treatment in advanced gastric or gastroesophageal junction adenocarcinoma is to prevent progression, extend survival and relieve symptoms with minimal adverse effects. Current treatment options for advanced gastric cancer include9,14,17:

- Chemotherapy – ECF (epirubicin, cisplatin and fluorouracil), EOF (epirubicin, oxaliplatin and fluorouracil), ECX (epirubicin, cisplatin and capecitabine), EOX (epirubicin, oxaliplatin and capcitabine), docetaxel and irinotecan, FOLFIRI (leucovorin, fluorouracil and irinotecan), mitomycin C and capcitabine.
- Biological therapy – trastuzumab (for HER2-positive disease).

EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>JOSHUA, NCT01461057, BP27836; pertuzumab, in combination with cisplatin, capecitabine and trastuzumab; phase II.</th>
<th>JACOB, NCT01774786, BP25114; pertuzumab vs placebo, both in combination with 5-fluorouracil, capecitabine, cisplatin and trastuzumab; phase III.</th>
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<tbody>
<tr>
<td>Sponsor</td>
<td>Hoffmann-La Roche.</td>
<td>Hoffmann-La Roche.</td>
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<tr>
<td>Status</td>
<td>Published.</td>
<td>Ongoing.</td>
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<tr>
<td>Source of information</td>
<td>Publication18, trial registry19, manufacturer.</td>
<td>Trial registry1, manufacturer.</td>
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<tr>
<td>Location</td>
<td>EU (not UK) and Republic of Korea.</td>
<td>EU (not UK), USA, Canada and other countries.</td>
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<td>Design</td>
<td>Randomised, uncontrolled.</td>
<td>Randomised, placebo-controlled.</td>
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<td>Participants</td>
<td>n=30; aged ≥18 yrs; adenocarcinoma of the stomach or gastroesophageal junction; HER2-positive; inoperable; locally advanced or metastatic; no prior</td>
<td>n=780 (planned); aged ≥18 yrs; adenocarcinoma of the stomach or gastroesophageal junction; HER2-positive; metastatic; no prior cytotoxic</td>
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<td><strong>treatment for advanced or metastatic disease; prior (neo)adjuvant therapy allowed if completed ≥6 mths before study enrolment; no prior platinum-based (neo)adjuvant therapy.</strong></td>
<td><strong>chemotherapy for advanced or metastatic disease.</strong></td>
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<td><strong>Schedule</strong></td>
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<td>Randomised to pertuzumab 840mg IV for cycle 1 (a cycle is 3 wks), followed by 420mg IV for cycles 2–6 (arm A); or pertuzumab 840mg IV for cycles 1–6 (arm B); both in combination with cisplatin 80 mg/m² IV once every 3 wks and capecitabine 1,000 mg/m² orally twice daily for 14 days in every cycle. All patients receive trastuzumab at 8 mg/kg for cycle 1, followed by 6 mg/kg for subsequent cycles.</td>
<td>Randomised to pertuzumab 840mg IV once every 3 wks; or placebo IV once every 3 wks; both in combination with 5-FU 800mg/m²/24 hrs IV by continuous infusion for 120 hrs (days 1-5) every 3 wks, (6 cycles) or capecitabine 1,000mg/m² orally twice daily, evening of day 1 to morning of day 15 (28 doses) every 3 weeks (6 cycles), and trastuzumab, 8mg/kg IV initial dose on day 1, followed by 6mg/kg IV every 3 weeks.</td>
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<td><strong>Follow-up</strong></td>
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<td>Active treatment with pertuzumab, trastuzumab, cisplatin and capecitabine for up to 6 cycles (18 wks) or continuation with trastuzumab until investigator-assessed disease progression or unmanageable toxicity, follow-up 41 mths.</td>
<td>Active treatment up to 6 cycles (18 wks). Some patients will continue to receive pertuzumab and trastuzumab; or pertuzumab placebo and trastuzumab until disease progression, unacceptable toxicity or withdrawal from the study for another reason. Follow-up up to 5 yrs after last dose.</td>
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<td><strong>Primary outcomes</strong></td>
<td><strong>Primary outcomes</strong></td>
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<td>Pharmacokinetics; adverse events (AEs).</td>
<td>Overall survival.</td>
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<td><strong>Secondary outcomes</strong></td>
<td><strong>Secondary outcomes</strong></td>
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<td>Exploratory efficacy endpoint to assess anti-tumour activity. No quality of life measurement included in trial outcomes.</td>
<td>Progression-free survival; objective response rates; duration of objective response; clinical benefit; AEs; incidence of left ventricular systolic dysfunction; European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30a; EQ-5Da; EORTC QLQ-STO22b; EQ-5Db.</td>
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<td><strong>Key results</strong></td>
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<td>Safety profiles were similar between arms and treatment was well tolerated; partial responses were achieved by 86% and 55% of patients in arms A and B, respectively.</td>
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<td><strong>Adverse effects (AEs)</strong></td>
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<td>The total number of grade ≥3 AEs was 78 in arm A and 60 in arm B. The most frequent grade ≥3 AEs were neutropenia, anaemia, diarrhoea, decreased appetite, febrile neutropenia, fatigue, hypokalaemia, hyponatraemia, nausea, stomatitis, hypophosphataemia and mucosal inflammation. 73% and 67% of patients in arms A and B, respectively, experienced at least one serious AE and the total number of all serious AEs was 35 in arm A and 19 in arm B. Serious AEs that occurred in ≥2 patients overall were diarrhoea, febrile neutropenia, acute renal failure, asthenia, fatigue, gastric</td>
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* A quality of life measure for cancer patients
  
* A modular supplement to QLQ-C30 for stomach cancer
  
* A standardised measure of health outcome providing a single index value for health status.
obstruction, hyponatraemia, mucosal inflammation, neutropenia, pneumonia, pulmonary embolism and vomiting. One serious AE in arm B (fungal pneumonia) resulted in death. This was considered by the investigator to be related to the chemotherapy agents. Two patients in arm A experienced asymptomatic left ventricular ejection fraction (LVEF) decline. After delaying study treatment, their LVEF values recovered and these patients continued receiving study treatment.

Expected reporting date - Study completion date reported as December 2021.

**ESTIMATED COST and IMPACT**

**COST**

Pertuzumab is already marketed in the UK for the treatment of breast cancer. A 420mg vial (30mg/mL) costs £2,39520.

**IMPACT - SPECULATIVE**

**Impact on Patients and Carers**

- Reduced mortality/increased length of survival
- Reduced symptoms or disability
- No impact identified
- Other

**Impact on Health and Social Care Services**

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

**Impact on Costs and Other Resource Use**

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

**Other Issues**

- Clinical uncertainty or other research question identified
- None identified

**REFERENCES**

1. ClinicalTrials.gov. A double-blind, placebo-controlled, randomized, multicenter phase III study evaluating the efficacy and safety of pertuzumab in combination with trastuzumab and