A double-blind, placebo-controlled, randomized, multicenter phase III study evaluating the efficacy and safety of pertuzumab in combination with trastuzumab and chemotherapy in patients with HER2-positive metastatic gastro-esophageal junction and gastric cancer

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON39981

Source
ToetsingOnline

Brief title
JACOB

Condition

- Other condition

Synonym
gastric and gastro-oesophageale adenocarcinoma, gastric cancer

Health condition

gemetastaseerde adenocarcinomen van de maag en de maagslokdarmovergang

Research involving
Human

Sponsors and support

Primary sponsor: Hoffmann-La Roche
Source(s) of monetary or material Support: F. Hoffmann - La Roche

Intervention

Keyword: HER2-positive advanced gastro-esophageal junction and gastric cancer, pertuzumab, trastuzumab

Outcome measures

Primary outcome

To compare OS in patients treated with pertuzumab in addition to cisplatin and

capecitabine (or 5-FU) versus patients treated with placebo in addition to the

standard of care regime.

Secondary outcome

The secondary objectives for this study are as follows:

* To compare investigator-assessed PFS, ORR, duration of objective response

(DoR), and clinical benefit rate (CBR) between the two treatment arms

* To compare the safety profile between the two treatment arms

* To assess the pharmacokinetics of pertuzumab

* To compare the patient-reported outcomes (PROs) of health-related quality of

life (HRQoL), GC, and treatment-related symptoms as measured by the European

Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and its GC

module, the QLQ-STO22, for patients in each treatment arm.

There are some *exploratory objectives' for this study, please be referred to

page 34 of the protocol.

Study description

Background summary

This study is designed to assess whether the addition of pertuzumab to the standard-of-care regimen will improve OS and have an acceptable safety profile in patients with HER2-positive, metastatic gastric or GEJ adenocarcinoma.

Pertuzumab blocks the HER2-receptors of the tumor to prevent signal transduction of the tumor cell, thus inhibiting tumorgrowth. Although both trastuzumab and pertuzumab bind to the HER2receptor, they have a different mode of action. Prior studies in HER2 positive breastcancer demonstrated the complementary effect of pertuzumab and trastuzumab.

The overall safety profile and increased antitumor efficacy provided by the addition of pertuzumab to treatment regimens composed of trastuzumab plus cytotoxic chemotherapeutic drugs has been established in Phase II and III trials in HER2-positive
breast cancer.

Study objective

Pertuzumab is the investigational agent being studied for the treatment of HER2-positive gastric cancer. This study is to compare the overall survival (OS) in patients treated with pertuzumab in addition to trastuzumab (Herceptin®) plus cisplatin and capecitabin (or 5-FU) versus patients treated with placebo in addition to the standard of care.

Study design

This is a double-blind, placebo-controlled, randomized, multicenter, international, comparative Phase III trial designed to evaluate the efficacy and safety of pertuzumab administered in conjunction with TFP combination therapy as first-line treatment in patients with HER2-positive metastatic adenocarcinoma of the stomach or gastroesophageal junction (GEJ), or both. Eligible patients will be randomized in a 1:1 ratio to receive either

investigational treatment with pertuzumab or placebo consisting of:
Arm A: Pertuzumab 840-mg given intravenously every 3 weeks (Q3W)
OR
Arm B: Pertuzumab placebo given intravenously Q3W

Eligible patients randomized to either arm will also be treated with the TFP combination for six treatment cycles (Cycles 1*6), consisting of:
* Trastuzumab 8 mg/kg initial dose (Day 1) followed by subsequent doses of 6 mg/kg, given intravenously Q3W
PLUS
* Cisplatin 80 mg/m2 given intravenously (Day 1 only) Q3W
PLUS
* Capecitabine 1000 mg/m2 taken orally twice a day (2000 mg/m2/24 hours) for a total of 28 doses (evening of Day 1 through morning of Day 15) Q3W
OR
5-fluorouracil (5-FU) 800 mg/m2/24 hours given intravenously by continuous infusion for 120 hours (Days 1*5) Q3W

Intervention

Eligible patients will be treated according to the schedule of assessment (table 1-1, page 120-121 of the protocol).

Study burden and risks

SIDE EFFECTS KNOWN TO BE ASSOCIATED WITH PERTUZUMAB AND TRASTUZUMAB

Common Side Effects (may occur in 10 or more out of 100 patients [>10%])
* Diarrhea
* Neutropenia (a reduction in white blood cells, which are needed to fight infection)
* Mucosal inflammation (inflammation of the lining of the mouth, digestive system, or genital tract)
* Decreased appetite
* Vomiting
* Abnormal sense of taste
* Anemia (a lack of red blood cells)
* Disorders of the nails
* Asthenia (physical weakness and lack of strength)
* Skin rashes
* Altered sensation in fingers and feet (neuropathy)
* Aching of the muscles or joints
* Infusion reaction with symptoms such as nausea, fever, diarrhea, chills, fatigue (easy tiring), and headache
* Colds or chest infections
* Dizziness

* Dry and/or itchy skin (pruritus)

Less Common Side Effects (may occur in 1 to 9 out of 100 patients [1% to <10%])
* Infections where the nail and skin meet at the side or the base of a finger or toenail (paronychia)
* Allergic/hypersensitivity reaction
* Accumulation of excess fluid between the two pleural layers that surround the lungs, which may cause breathlessness
* Inadequate pumping of the heart; symptoms may include breathlessness, easy tiring, swelling of the ankles or feet, and persistent coughing

Rare but Serious Side Effects (may occur in <1 out of 100 patients)
* Heart failure
* Severe allergic reaction (anaphylaxis)

The study procedures and treatments may be associated with risks and may cause discomfort. There is a risk of slight pain or bruising when blood is collected. Undergoing CT/ PET scans exposes the patients to low dose of radiation. The dye used in some CT scans may cause serious allergic reactions that can be life-threatening without treatment.

There may also occur side effects that are still unknown. The other (standard) already registered chemotherapeutic agents (capecitabine, cisplatin, 5-FU) used in this study, could also cause side effects.

Contacts

Public
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Disease-Specific Inclusion Criteria;1. Histologically confirmed (by enrolling center) metastatic adenocarcinoma of the stomach or GEJ;2. HER2-positive tumor defined as either IHC 3+ or IHC 2+, the latter in combination with ISH+, as assessed by a sponsor-designated central laboratory on a primary or metastatic tumor;Note: ISH positivity is defined as a ratio of * 2.0 for the number of HER2 gene copies to the number of signals for chromosome 17 centromere (CEP17). For IHC scoring, the cutoffs as approved by the Food and Drug Administration (FDA) in the context of ToGA apply. Availability of formalin-fixed paraffin-embedded (FFPE);representative tumor tissue for central confirmation of HER2 is mandatory. (See Section 4.5.1.1 for further details.);3. Measurable or evaluable non-measurable disease as assessed by the investigator, according to RECIST v1.1; see Appendix 3.;4. Eastern Cooperative Oncology Group (ECOG) PS 0 or 1;5. Life expectancy * 3 months;General Inclusion Criteria;6. Age* 18 years;7. Ability to comply with requirements of the protocol, as assessed by the investigator;8. Signed Informed Consent document

Exclusion criteria

Cancer-Related Exclusion Criteria;
1. Previous systemic cytotoxic chemotherapy for advanced (metastatic) disease;
2. History of exposure to the following cumulative doses of anthracyclines;
a. Epirubicin >720 mg/m2;
b. Doxorubicin or liposomal doxorubicin > 360 mg/m2;
c. Mitoxantrone > 120 mg/m2 or idarubicin >90 mg/m2;
d. Other (e.g., liposomal doxorubicin or other anthracycline greater than the equivalent of 360 mg/m2 of doxorubicin);
e. If more than one anthracycline has been used, then the cumulative dose must not exceed the equivalent of 360 mg/m2 of doxorubicin.;
3. Evidence of disease progression documented within 6 months after completion of prior neoadjuvant or adjuvant cytotoxic chemotherapy, or both, or radiotherapy for gastric or GEJ adenocarcinoma;
4. Previous treatment with any HER2-directed therapy, at any time, for any duration;
5. Previous exposure to any investigational treatment within 30 days before the first dose of

study treatment;
6. Radiotherapy within 30 days before the first dose of study treatment (within 2 weeks if given as palliation to bone metastases, if recovered from all toxicities);
7. History or evidence of brain metastasis;
8. Clinically significant active GI bleeding (Grade * 2 according to NCI CTCAE v4.03);
9. Residual toxicity resulting from previous therapy (e.g., hematologic, cardiovascular, or neurologic toxicity that is Grade * 2). Alopecia is permitted;
10. Other malignancy (in addition to GC) occurring within 5 years before enrollment, except for carcinoma in situ of the uterine cervix or squamous or basal cell carcinoma of the skin that has been previously treated with curative intent Clinical Laboratory Exclusion Criteria (must be confirmed within 7 days before first dose of study treatment);
11. Absolute neutrophil count (ANC) >1.5 × 109/L;
12. Platelet count >75 × 109/L;
13. Hemoglobin >9.0 g/dL;
14. Creatinine CL >60 mL/min (Cockcroft-Gault Formula, see Appendix 6);
15. Serum bilirubin (total) >1.5 × upper limit of normal (ULN) of laboratory normal range; in case of known Gilbert disease a total bilirubin of up to 2 × ULN is permitted.;
16. AST, ALT, and alkaline phosphatase (ALP) parameters;
a) In patients with no liver and no bone metastases;
i. AST or ALT >1.5 × ULN, and ALP >2.5 ×ULN;
ii. AST or ALT > 2.5 ×ULN;
b) In patients with liver metastases and no bone metastases;
i. AST or ALT >5 × ULN, and ALP >2.5 ×ULN;
c) In patients with liver metastases and bone metastases;
i. AST or ALT > 5 × ULN, and ALP > 10×ULN;
d) In patients with bone metastases and no liver metastases;
i. AST or ALT > 1.5 × ULN, and ALP > 10 ×ULN;
17. Serum albumin >25 g/L;
18. Serum pregnancy test positive in a female patient of childbearing potential;
General Exclusion Criteria;
19. Documented history of congestive heart failure (CHF) of any New York Heart Association (NYHA) criteria (see Appendix 5);
20. Angina pectoris requiring treatment;
21. Myocardial infarction within the past 6 months before the first dose of study treatment;
22. Clinically significant valvular heart disease or uncontrollable high-risk cardiac arrhythmia (i.e., atrial tachycardia with a heart rate >100/min at rest), significant ventricular arrhythmia (ventricular tachycardia) or higher-grade atrioventricular-block;
(second degree AV-block Type 2 [Mobitz 2] or third degree AV-block);
23. History or evidence of poorly controlled arterial hypertension (systolic blood pressure > 180 mmHg or diastolic blood pressure >100 mmHg);
24. Baseline LVEF value > 55%, assessed by echocardiogram [ECHO], multigated acquisition (MUGA) scan, or cardiac magnetic resonance imaging (MRI) scan;
25. Dyspnea at rest due to complications of advanced malignancy or other disease or requirement of supportive oxygen therapy;
26. Any significant uncontrolled intercurrent systemic illness (e.g., active infection, poorly controlled diabetes mellitus);
27. Previous major surgery within 30 days before the first dose of study treatment, unless

completely recovered;
28. Known infection with HIV, hepatitis B virus, or hepatitis C virus that requires active treatment;
29. Ongoing chronic treatment or high-dose treatment with corticosteroids. Inhaled steroids, topical steroids and clinically indicated short courses of oral steroids are permitted.;
30. Known dihydropyrimidine dehydrogenase (DPD) deficiency;
31. Known hypersensitivity to any component of study treatment;
32. Current use of antiviral drug sorivudine or its chemically related analogs, such as brivudine;
33. Lactating female patient;
34. Any patient unwilling or unable to use adequate contraceptive measures (as described in Section 5.2.3) during study treatment and for at least 7 months after the last dose of pertuzumab or trastuzumab, except for a patient with documented surgical sterilization or a postmenopausal female

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	05-03-2014
Enrollment:	3
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Cisplatin

Generic name:	cisplatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Herceptin
Generic name:	trastuzumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Perjeta
Generic name:	pertuzumab
Product type:	Medicine
Brand name:	Xeloda
Generic name:	capecitabine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	03-01-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-05-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-05-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-06-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-12-2013
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-02-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-05-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-09-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-11-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-11-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-12-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-01-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-02-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-02-2017
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-04-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-04-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-10-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-10-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-12-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-04-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-12-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-12-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-03-2019
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2012-003554-83-NL
Other	Het onderzoek is onder het EudraCT nummer terug te vinden op www.rochetrials.com, zodra de studie is goedgekeurd.
CCMO	NL42759.018.12