# INtegratioN of trastuzumab, with or without pertuzumab, into periOperatiVe chemotherApy of HER-2 posiTIve stOmach caNcer: the INNOVATION-TRIAL

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To increase the major pathological response rate (< 10% vital tumor cells) to neoadjuvant treatment by integrating both trastuzumab and pertuzumab into perioperative chemotherapy for HER-2 positive, resectable gastric cancer.

| | |
|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Completed |
| **Health condition type** | Gastrointestinal neoplasms malignant and unspecified |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON53087

**Source**
ToetsingOnline

**Brief title**
INNOVATION

### Condition

- Gastrointestinal neoplasms malignant and unspecified

**Synonym**
stomach cancer

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** European Organisation for Research in Treatment of Cancer (EORTC)

**Source(s) of monetary or material Support:** EORTC,Roche

## Intervention

**Keyword:** Her2 positive, pertuzumab, stomach cancer, trastuzumab

## Outcome measures

### Primary outcome

The primary endpoint is major pathological response rate (< 10% vital residual

tumor cells).

### Secondary outcome

Secondary endpoints are:

* R0 resection rate

* Pathological complete response

* Locoregional failure

* Distant failure

* Progression-free survival according to RECIST v1.1

* Recurrence-free-survival (from surgery)

* Overall survival

* Adverse event assessment according to CTCAE v 4.0

# Study description

### Background summary

With an estimated almost one million cases in 2012, gastric cancer is currently the 5th most common malignancy and the third leading cause of cancer-related mortality worldwide (Ref. 1). Approximately 25% of all patients with gastric cancer have resectable disease at presentation. Even for patients with localized gastric or gastroesophageal junction adenocarcinoma, the prognosis is poor in *Western* countries with 5-year survival rates of approximately 35 %

after standard perioperative chemotherapy followed by curative surgery (Ref. 2, Ref. 9). Between 10 and 20% of patients in clinical trials for gastric and gastroesophageal cancer are HER-2 positive (Ref. 3; Ref. 4). However, several epidemiological studies observed lower rates of HER-2 positive disease (Ref. 5). In advanced gastric and gastroesophageal cancer, the addition of trastuzumab to standard chemotherapy has significantly improved progression-free survival, overall survival, and response rates (Ref. 3). In HER-2 positive breast cancer, the addition of trastuzumab to standard neoadjuvant chemotherapy significantly improves both, pathological complete response rates and overall survival (Ref. 6). A further significant improvement of histopathological complete response rates after neoadjuvant treatment of HER-2 positive breast cancer has been observed recently; when the dimerization inhibitor pertuzumab was added to trastuzumab and chemotherapy (pathological complete response rates 29% versus 45%) (Ref. 7). In advanced breast cancer, the addition of pertuzumab to trastuzumab and docetaxel increased progression-free survival from 12.4 to 18.5 months (HR 0.62; 95% CI 0.51-0.75; p<0.001) (Ref. 8). With respect to targeted, perioperative treatment of HER-2 positive gastric and gastroesophageal junction cancer there is neither clinical trial data available, nor a randomized clinical trial ongoing.
In view of the significant benefit of the addition of trastuzumab and pertuzumab to the neoadjuvant treatment of breast cancer, this study has been developed to address to potential added value of a perioperative treatment regimen which integrates HER-2 targeting drugs for gastric and gastroesophageal junction cancer.

**Study objective**

To increase the major pathological response rate (< 10% vital tumor cells) to neoadjuvant treatment by integrating both trastuzumab and pertuzumab into perioperative chemotherapy for HER-2 positive, resectable gastric cancer.

**Study design**

This is a randomized phase II trial with a 1:2:2 randomization (control: experimental arm 1: experimental arm 2). Potentially eligible patients will be screened centrally for HER-2 status. After confirmation of HER-2 positive disease, eligible patients will be centrally randomized through the EORTC randomization system. A minimization technique will be used for random treatment allocation between the three treatment arms. Stratification will be done by Asia versus Europe; GEJ versus GC (non-GEJ); HER-2 IHC 3+ versus IHC2+/FISH+; intestinal versus non-intestinal; and chemotherapy regimen (Cisplatin+Capecitabine/5-FU /CapOx/mFOLFOX6/FLOT).

Standard arm: chemotherapy alone

-- FLOT is administered in cycles of 2 weeks for 4 cycles (= 8 weeks) on day 1, 15, 29 and 43 pre- and postoperatively.
- CapOx is given for 3 cycles of 3 weeks (= 9 weeks) on day 1, 22 and 43 pre- and postoperatively.
- mFOLFOX6 is given for 4 cycles of 2 weeks (=8 weeks) on day 1, 15, 29 and 43 pre- and postoperatively

Experimental arms (neoadjuvant and adjuvant treatment)
Experimental arm 1: chemotherapy as in the control group, plus trastuzumab (8 mg/kg loading dose, followed by 6 mg/kg every 3 weeks) at day 1, independent of the chemotherapy regimen chosen for 3 cycles of 3 weeks before and after surgery.

Experimental arm 2: chemotherapy plus trastuzumab as in experimental arm 1, plus pertuzumab (840 mg every 3 weeks) at day 1, independent of the chemotherapy regimen chosen. In the absence of contraindications after completion of adjuvant treatment, maintenance treatment with trastuzumab /trastuzumab and pertuzumab will continue.

**Intervention**

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**Study burden and risks**

Trastuzumab and pertuzumab are no standard treatments in adjuvant therapy. Both treatment could cause a benefit for the patient an increase the pathological response rate and could affect progression-free survival and overall survival

positively.Due to pertuzumab is an small risk for an increase in ejection fraction.

# Contacts

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BE

# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)

## Inclusion criteria

* All patients (HER-2 positive and negative) should be registered in the trial as soon as possible after written informed consent for screening according to ICH/GCP, and national/local regulations.
* Histologically proven, gastric or GE-junction adenocarcinoma (Siewert I-III)
* Absence of distant metastases on CT scan of thorax and abdomen
* Patient medically fit for gastrectomy/oesophagectomy as decided by the investigator
* Age >= 18 years
* WHO performance status 0 - 1,

Randomization:
- HER-2 overexpression, as determined by central testing using immunohistochemistry (IHC 3+) or the combination of IHC 2+ and HER-2 FISH positive.
* Amenable to gastrectomy/oesophagectomy with curative intent as confirmed by a multidisciplinary team discussion
* UICC (7th edition) tumor stage Ib to III, as defined by CT scan and/or MRI. Endosonography (EUS) is recommended, but not mandatory. EUS should especially be considered to distinguish T1 and T2 tumors and to evaluate local resectability. (In case of conflicting results of CT scan and/or MRI and endoscopic ultrasound, the final decision on which finding the staging is based should be taken by the multidisciplinary team).
- The cardiac ejection fraction (LVEF), as determined by echocardiography, MUGA or cardiac MRI should be at least 55%.
* Adequate organ function:
* White blood cell count (WBC) > 3 x 109/L
* Absolute neutrophil count (ANC) > 1.5 x 109/L
* Platelets >= 100 x 109/L
* Hemoglobin >= 9 g/dL (transfusions are permitted to reach this value)
* Estimated glomerular filtration rate (eGFR) according to MDRD should be > 50 ml/min for patients treated with oxaliplatin-based regimens upfront
Note: for patients that will receive CISPLATIN upfront, a GFR > 60 ml/min is required
* Total bilirubin within normal limits (if the patient has documented Gilbert*s disease <= 1.5 × ULN or direct bilirubin <= ULN)
* Aspartate transaminase (AST) and alanine transaminase (ALT) <= 2.5 × ULN
- Absence of preexisting neuropathy > grade I
- Investigator and patient have to agree to replace any oral anticoagulations by subcutaneous administration of low-molecular weight heparin
- Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with study protocol & follow-up schedule;
- For women who are not postmenopausal (> 12 months of nontherapy induced amenorrhea)or surgically sterile(absence of ovaries and/or uterus):
- agreement to remain abstinent or use single or combined contraceptive methods that result in a failure rate of < 1% per year during treatment period &for at least 7 months after last
treatment dose
- Negative serum pregnancy test
- For men: agreement to remain abstinent or use a condom plus additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period &for at least 7
months after last dose of study treatment.

### Exclusion criteria

* No prior chemo- or antibody therapy
* No history of significant cardiac disease defined as:
* Symptomatic CHF (NYHA classes II-IV, see Appendix D)
* High-risk uncontrolled arrhythmias, i.e. atrial tachycardia with a heart rate > 100/min at rest, significant ventricular arrhythmia (ventricular tachycardia) or higher-grade AV-block (second degree AV-block Type 2 [Mobitz 2] or third degree AV-block)
* History of myocardial infarction within 6 months prior to randomization
* Clinically significant valvular heart disease
* No central nervous system metastasis or leptomeningeal tumor spread. For patients without any neurological symptoms, a brain MRI is recommended, but not obligatory. For patients with any clinical symptoms which may be attributed to brain metastases, a brain MRI is compulsory to rule out cerebral metastases.
* No known hypersensitivity to the components of trastuzumab, pertuzumab, cisplatin, oxaliplatin, docetaxel, 5-FU or capecitabine
- no patients with interstitial lung disease
* Absence of preexisting neuropathy > grade I
* No known dihydropyrimidine dehydrogenase (DPD) deficiency (testing not required). In case of specific recommendations due to institutional and/or national guidelines please proceed accordingly.
* No ongoing or concomitant use of the antiviral drug sorivudine or its chemically related analogs, such as brivudine
* No chronic treatment with high-dose intravenous corticosteroids (> 10 mg/day prednisone equivalents)
* No previous malignancy within the last 5 years, with the exception of adequately treated cervical carcinoma in situ, localized non-melanoma skin cancer, or other curatively treated cancer without impact on the patient*s overall prognosis according to the judgment of the investigator.
* Female patients should not be breast feeding.

## Study design

### Design

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| Study phase: | 2 |
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Open (masking not used) |

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|---|---|
| Control: | Active |
| Primary purpose: | Treatment |

## Recruitment

NL

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|---|---|
| Recruitment status: | Completed |
| Start date (anticipated): | 21-07-2020 |
| Enrollment: | 4 |
| Type: | Actual |

## Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | 5-fluorouracil |
| Generic name: | 5-FU |
| Registration: | Yes - NL intended use |
| 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 |
| Registration: | Yes - NL outside intended use |
| Product type: | Medicine |
| Brand name: | xeloda |
| Generic name: | capecitabine |
| Registration: | Yes - NL intended use |

# Ethics review

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|---|---|
| Approved WMO Date: | 01-04-2015 |
| Application type: | First submission |
| Review commission: | METC NedMec |
| Approved WMO Date: | 04-01-2017 |
| Application type: | Amendment |
| Review commission: | METC NedMec |
| Approved WMO Date: | 26-02-2019 |
| Application type: | First submission |
| Review commission: | METC NedMec |
| Approved WMO Date: | 03-07-2019 |
| Application type: | Amendment |
| Review commission: | METC NedMec |
| Approved WMO Date: | 15-07-2019 |
| Application type: | Amendment |
| Review commission: | METC NedMec |
| Approved WMO Date: | 02-10-2019 |
| Application type: | Amendment |
| Review commission: | METC NedMec |
| Approved WMO Date: | 12-05-2020 |
| Application type: | Amendment |
| Review commission: | METC NedMec |
| Approved WMO Date: | 11-06-2020 |
| Application type: | Amendment |
| Review commission: | METC NedMec |
| Approved WMO Date: | 19-03-2022 |
| Application type: | Amendment |
| Review commission: | METC NedMec |
| Approved WMO | |

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|---|---|
| Date: | 07-06-2022 |
| Application type: | Amendment |
| Review commission: | METC NedMec |
| Approved WMO Date: | 27-01-2023 |
| Application type: | Amendment |
| Review commission: | METC NedMec |
| Approved WMO Date: | 13-02-2023 |
| Application type: | Amendment |
| Review commission: | METC NedMec |
| Approved WMO Date: | 30-12-2023 |
| Application type: | Amendment |
| Review commission: | METC NedMec |
| Approved WMO Date: | 16-04-2024 |
| Application type: | Amendment |
| Review commission: | METC NedMec |

# 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 | EUCTR2014-000722-38-NL |
| ClinicalTrials.gov | NCT02205047 |

| Register | ID |
| --- | --- |
| CCMO | NL51319.031.15 |