Feasibility study of chemoradiation, TRAstuzumab and Pertuzumab in resectable HER2+ esophageal carcinoma: the TRAP study

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Assess the feasibility of preoperative treatment with pertuzumab and trastuzumab combined with preoperative chemoradiation (carboplatin, paclitaxel and radiation) in terms of withdrawal rate from surgery

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON41623

Source
ToetsingOnline

Brief title
TRAP

Condition

- Gastrointestinal neoplasms malignant and unspecified

Synonym
Esophageal carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum

Source(s) of monetary or material Support: Roche

Intervention

Keyword: Her2+, Pertuzumab, Resectabel esophageal carcinoma, Trastuzumab

Outcome measures

Primary outcome

Feasibility of preoperative treatment with pertuzumab and trastuzumab combined with preoperative chemoradiation (carboplatin, paclitaxel and radiation) in terms of withdrawal rate from surgery

Secondary outcome

• To assess toxicities of pertuzumab and trastuzumab alone and in combination with chemoradiation.

• To assess post-operative complications.

• To assess pathological response.

• To assess R0 resection rate.

• To assess pharmacokinetics of pertuzumab and trastuzumab

Study description

Background summary

Despite neoadjuvant chemoradiation regimens, resectable esophageal cancer remains a disease with poor outcome. The clinical benefit of HER2 targeting with trastuzumab has been shown in the setting of advanced disease and the safety of combining trastuzumab with chemoradiation in the curative setting has been established. In breast cancer, the added value of pertuzumab to standard treatment with trastuzumab has been shown both in the neoadjuvant and the metastastic setting. Taken together, there is a sound rationale to explore the combination of radiotherapy plus chemotherapy with trastuzumab and pertuzumab in HER2+ resectable esophageal cancer. However, since the number of HER2+ patients in this setting is limited, and no data are available on the safety of

this combination prior to major surgery, we propose to first conduct a feasibility study with this treatment strategy. When the results of this study show that this treatment strategy does not compromise the planned surgery, we will subsequently design a prospective study with efficacy as primary endpoint.

Study objective

Assess the feasibility of preoperative treatment with pertuzumab and trastuzumab combined with preoperative chemoradiation (carboplatin, paclitaxel and radiation) in terms of withdrawal rate from surgery

Study design

This is a non-randomized feasibility study a feasibility study with Paclitaxel (T), Carboplatin (C), Pertuzumab (P), Trastuzumab (H), and radiation (RT) followed by surgical resection of the oesophagus.

Intervention

Paclitaxel 50 mg/m2 and Carboplatin AUC = 2 will be given by intravenous infusion on days 1, 8, 15, 22 and 29. Trastuzumab will be administered at a dose of 4 mg/kg on day 1, followed by 2 mg/kg at wk 2-6. From wk 7 onwards trastuzumab is administered at a dose of 6 mg/kg every 3 weeks. Pertuzumab will be given 840 mg intravenously at each administration.
Thus, trastuzumab and pertuzumab will be continued during eight weeks after the end of chemoradiation. Surgery will be planned in or around week 14, approximately eight weeks after the end of chemoradiation.

Study burden and risks

Trastuzumab and pertuzumab will be continued during eight weeks after the end of chemoradiation.
Both the blood sample as the intravenous drip may be slightly painful and cause a bruise at the puncture site . Furthermore, side effects occur, as a result of pertuzumab and trastuzumab.
During an infusion of pertuzumab and trastuzumab chills, fever and other flu-like symptoms may occur. The following symptoms are particularly with pertuzumab very common : diarrhea , decrease in white blood cells , mucosal inflammation, decreased appetite , vomiting , different taste perception, anemia , diseases of the nails, physical weakness , rash , discomfort in the fingers and feet , muscle pain , joint pain , colds or chest infections , dizziness and dry or itchy skin.

Heart problems can sometimes occur during treatment and sometimes after treatment and can be severe. They include weakening of the heart muscle (which

can lead to heart failure), inflammation of the pericardium , and cardiac arrhythmias. This can lead to symptoms such as shortness of breath (including overnight) cough , fluid retention (swelling) in the legs or arms . In rare cases , patients treated with pertuzumab and trastuzumab had suffered from heart failure .

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Histologically proven adenocarcinoma of the intrathoracic esophagus or gastro esophageal junction.
- HER2-positive tumor defined as either IHC 3+ or IHC 2+, the latter in combination with ISH+, as assessed by the sponsor-designated central laboratory (pathology AMC) on a primary tumor biopsy.

- Surgical resectable (T2-3, N0or N+, M0), as determined by Endoscopic Ultra Sound (EUS) and CT scan of neck, thorax and abdomen. Tumors that cannot be passed with an endoscope for endoscopic ultrasound are eligible if all other criteria are fulfilledT1N+ tumors are eligible, T1N0 tumors and in situ carcinoma are not eligible.
- Tumor length longitudinal <= 10 cm; if larger than 10 cm, inclusion should be discussed with the principal investigator .
- If tumor extends below the gastroesophageal (GE) junction into the proximal stomach, the bulk of the tumor must involve the esophagus or GE junction. The tumor must not extend more than 2 cm into the stomach.
- No invasion of the tracheobronchial tree or presence of tracheoesophageal fistula.
- Age >= 18 years.
- ECOG performance status 0 or 1.
- Adequate hematological, renal and hepatic functions defined as:
o neutrophiles >= 1.5 x 109/L
o platelets >= 100 x 109/L
o hemoglobin >= 5.6 mmol
o total bilirubin <= 1.5 x upper normal limit
o creatinine clearance (Cockroft) > 60 ml/min
- Adequate left ventricular ejection fraction defined as an LVEF of >=55%.
- Written, voluntary informed consent.

Exclusion criteria

- A tumour the epicenter of which in the stomach is greater than 5 cm of the GE junction or those within 5 cm of the GE junction without extension in the oesophagus are classified as gastric cancer.
- Past or current history of malignancy other than entry diagnosis interfering with prognosis of esophageal cancer
- Pregnancy (positive serum pregnancy test), planning to become pregnant, and lactation.
- Patient (male or female) is not willing to use highly effective methods of contraception (per institutional standard) during treatment and for 6 months (male or female) after the end of treatment.
- Previous chemotherapy, radiotherapy, treatment with an anti-HER2 antibody or with small molecule HER2 inhibitors.
- Clinically significant cardiovascular disease (including myocardial infarction, unstable angina, symptomatic congestive heart failure, serious uncontrolled cardiac arrhythmia) <= 1 year before randomization.
- Pulmonary fibrosis and/or severely impaired lung function.
- Pre-existing motor or sensory neurotoxicity greater than WHO grade 1.
- Active infection or other serious underlying medical condition which would impair the ability of the patient to receive the planned treatment, including prior allergic reactions to drugs containing Cremophor, such as teniposide or cyclosporine.
- Dementia or altered mental status that would prohibit the understanding and giving of informed consent

- Inadequate caloric- and/or fluid intake.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	28-04-2014
Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Herceptin
Generic name:	Trastuzumab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Perjeta
Generic name:	Pertuzumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	03-01-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO Date:	11-03-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-04-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-04-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-05-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-06-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-09-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-10-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-10-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-06-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	29-07-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-12-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-03-2016
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	EUCTR2013-004111-42-NL
CCMO	NL46460.018.13