Patients with ADAM12 > 203 ng/mL in their serum benefit from the addition of biweekly tocilizumab for 3 doses to neoadjuvant chemoradiation before esophagectomy.

**Ethical review**  
Approved  
**Status**  
Pending  
**Health condition type**  
-  
**Study type**  
Interventional

**Summary**

**Brief title**

BASALT

**Health condition**

Esophageal adenocarcinoma

**Sponsors and support**

Primary sponsor: Investigator-initiated, sponsored by Oncode Institute  
Source(s) of monetary or material Support: Oncode Institute

**Intervention**

**Outcome measures**

**Primary outcome**

The primary objective of this study is to demonstrate that stroma-targeting by tocilizumab in esophageal adenocarcinoma patients with highly activated stroma increases efficacy of chemoradiotherapy measured by pathological response according to the Mandard criteria. Patients will be grouped for ADAM12, a non-invasive blood-borne marker of stromal activation.
Secondary outcome

- Efficacy and mechanism of action of tocilizumab with neoadjuvant chemoradiation against esophagogastric cancer by:
  - R0 resection rate
  - Progression free survival
  - Overall survival
  - IL6 STAT3 pathway inhibition measured by gene expression analysis
  - Levels of IL-6 in serum.
  - Phosphorylated STAT3 and stromal abundance measured by immunohistochemistry in formalin-fixed paraffin-embedded tumor tissue
  - Levels of ADAM12 in tumor biopsies and serum.
  - Incidence and severity of toxicity defined according to CTCAE v5.0 and Radiation Oncology Group (RTOG) criteria.
  - Incidence and severity of post-operative complications according to the Clavien - Dindo classification.
  - Percentage completion of chemotherapy and radiation treatment.
  - Percentage withdrawal rate from surgery due to tocilizumab related complications.
  - Percentage delay of surgery due to tocilizumab related complications.

Study description

Background summary

Esophageal adenocarcinoma continues to have a poor prognosis despite intensive treatment regimes of chemoradiation and resection. The tumor stroma has increasingly been found to harbor tumor-promoting properties. Recently, serum ADAM12 has been found as a marker for active stroma. In a recent preclinical study, active stroma was found to confer resistance to chemoradiation in esophageal adenocarcinoma via IL-6 production. Therefore, stroma-derived IL-6 provides an interesting new target for improvement of treatment. Tocilizumab is an IL6R inhibitor used in rheumatoid arthritis and cytokine-release syndrome. We aim to combat stromal induced therapy resistance in a personalized way using ADAM12 as a marker for stromal activation.

We designed a randomized proof-of-concept study with tocilizumab and standard of care paclitaxel, carboplatin and radiation followed by surgical resection of the oesophagus. Patients will be grouped for serum ADAM12 and randomized to receive tocilizumab or not in addition to standard of care paclitaxel, carboplatin and radiation. Given the lack of data for power calculation, the number of patients will be based on the rule-of-thumb estimate of n=12 in each arm. The cut-off value for ADAM12 will be 203 ng/mL. Paclitaxel 50 mg/m2 and...
carboplatin AUC = 2 will be given intravenously (i.v.) on days 1, 8, 15, 22 and 29. Tocilizumab will be given i.v. every two weeks on day 1, 15 and 29 at a dose 8 mg/kg with a maximum of 800 mg. Surgery will take place approximately eight to ten weeks after the end of chemoradiation in week 13-15. It is expected that accrual will be completed within 34 months.

**Study objective**

Patients with ADAM12 > 203 ng/mL in their serum benefit from the addition of biweekly tocilizumab for 3 doses to neoadjuvant chemoradiation before esophagectomy

**Study design**

Weekly visits during neoadjuvant chemoradiation, visit at surgery and 3 months after surgery

**Intervention**

tocilizumab

**Contacts**

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**Eligibility criteria**
Inclusion criteria

- Histologically proven adenocarcinoma of the esophagus or gastroesophageal junction.
- Surgical resectability (> 60 ml/min)
- Written, voluntary informed consent
- Patients must be accessible to follow up and management in the treatment center

Exclusion criteria

- Past (within 5 years) or current history of malignancy other than entry diagnosis interfering with prognosis of esophageal cancer, not including superficial and adequately treated skin and cervical malignancies.
- Previous chemotherapy, radiotherapy and/or treatment with IL-6 receptor blockers for esophageal cancer
- Previous radiation to the mediastinum precluding full dose radiation of the currently present esophageal tumor.
- Previous chemotherapy and/or treatment with targeted agents and/or IL-6 receptor blockers for other forms of cancer within the last six months.
- Invasion of the tracheobronchial tree or presence of tracheoesophageal fistula.
- T1N0 tumors or in situ carcinoma.
- 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.
- Clinically significant cardiovascular disease (including myocardial infarction, unstable angina, symptomatic congestive heart failure, serious uncontrolled cardiac arrhythmia) precluding major surgery.
- Pulmonary fibrosis and/or severely impaired lung function precluding major surgery.
- 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 despite consultation of a dietician and/or tube feeding.
- Requires systemic treatment with IL6 receptor blockers or IL-6 antagonists, TNF-alpha blockers or other biologicals within the last six months before the first dose of trial treatment.
- Has evidence of interstitial lung disease or active, non-infectious pneumonitis.
- Has an active infection requiring systemic therapy which has not resolved 3 days (simple infection such as cystitis) to 7 days (severe infection such as pyelonephritis) prior to the first dose of trial treatment.
- Has a total cholesterol > 6.5 mmol/L despite adequate treatment with lipid-lowering agents.
- Has evidence of (latent) tuberculosis infection in patient history.
Study design

Design

Study type: Interventional
Intervention model: Parallel
Allocation: Randomized controlled trial
Masking: Open (masking not used)
No intervention arm: N/A, unknown

Recruitment

NL
Recruitment status: Pending
Start date (anticipated): 16-11-2020
Enrollment: 48
Type: Anticipated

IPD sharing statement

Plan to share IPD: Undecided

Plan description

This will be described later if applicable

Ethics review

Approved
Date: 27-10-2020
Application type: First submission

Study registrations

(Historical) registrations known in this register
No registrations found

**In other registers**

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**Study results**

**Summary results**

To be determined