A phase I trial testing TH-302, a tumor-selective Hypoxia-Activated cytotoxic Prodrug, in combination with preoperative chemoradiotherapy in patients with distal esophageal and esophago-gastric junction adenocarcinoma

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Primary objective *To determine Maximum Tolerated Dose (MTD) of TH-302 combined with chemoradiotherapy (23 x1.8 Gy in combination with Carboplatinum and Paclitaxel) in patients with distal esophageal or esophago-gastric junction adenocarcinoma, and...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Gastrointestinal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON41947

Source
ToetsingOnline

Brief title
TH-302 in esophagal cancer

Condition

- Gastrointestinal neoplasms malignant and unspecified

Synonym
esophageal cancer

Research involving
Human

Sponsors and support

Primary sponsor: Medisch Universitair Ziekenhuis Maastricht
Source(s) of monetary or material Support: Maastro-Atrium Grant

Intervention

Keyword: esophagal adenocarcinoma, Phase I, TH-302

Outcome measures

Primary outcome

Incidence of

*Uncommon grade 3 or higher non-hematological toxicity (according to CTCAE v4.0 see appendix) except for esofagitis where grade III toxicity is already an acceptable toxicity in up to 10% of patients. We accept in this phase I study a grade III esophagitis of 50%. We accept grade 3 nausea and emesis unless standard anti-emetics have been used.

*Grade 4 or higher hematological toxicity (according to CTCAE v4.0)

*Grade 4 or higher postoperative toxicity within 30 days post-surgery according to the Clavien-Dindo classification . For anastomic leakage we accept a grade IV of 50% and for cardiorespiratory complications up to 30% grade IV will be

*Any grade 2 or higher non-hematologic toxicity except for esophagitis that does not resolve to grade 0 or 1 toxicity by the start of the next cycle of chemotherapy which, in judgment of the investigator or sponsor is considered a DLT

*Inability to begin the next cycle of chemotherapy of treatment within two

weeks of the last dose due to unresolved toxicity

Secondary outcome

*Presence of hypoxia response based on quantifiable changes in hypoxia

calculated from HX4 images at baseline compared to those at first

administration TH-302 (before chemoradiotherapy).

*Presence of anti-tumor activity measured by the rate of pathological Complete

Remission (pCR), histopathologic negative circumferential resection margin

(CRM) rate, local and distance recurrence rate, progression free and overall

survival, metabolic response one month after treatment.

*Correlation between HX4 PET/CT-scans and serum biomarker expression

Study description

Background summary

Combining TH-302 with chemo-radiotherapy will lead to:
*Direct cytotoxic effect of TH-302 on hypoxic cells of the primary tumor without enhancing normal tissue toxicity.
*Increase the sensitivity of the primary tumour to chemo-radiotherapy by decreasing the hypoxic fraction.
*A bystander cytotoxic effect of TH-302 on normoxic cells adjacent to hypoxic cells of the primary tumor.
*A potential cytotoxic effect on micrometastasis.

Study objective

Primary objective
*To determine Maximum Tolerated Dose (MTD) of TH-302 combined with chemoradiotherapy (23 x1.8 Gy in combination with Carboplatinum and Paclitaxel) in patients with distal esophageal or esophago-gastric junction adenocarcinoma, and consequently find the recommended Phase II dose (RP2D).
Secondary objective
*To explore the prognostic and predictive value on outcome of the repeated hypoxia PET/CT-scan at baseline and after administration of TH-302 (before start of RCT) .

*To determine presence of anti-tumor activity with TH-302 administration.
To explore the relationship between tumour hypoxia detected by the HX4 PET/CT-scans and serum biomarker expression: HIF-1, VEGF, CAIX, CD44, microRNA-210 and osteopontin expression

Study design

Open-label, single-center phase 1 study of an investigational agent TH-302 and standard chemoradiotherapy with a 3+3 dose escalation design through 3 dose levels.

Intervention

3 cohorts of patients will receive TH-302 in escalating doses during standard chemo-radiotherapy Extra patients can be added to a cohort in case of dose limiting toxicity, resulting in a maximum of 6 patients per dose level. Each patient included will have HX4 imaging before (d1) and after the first dosage of TH-302 (d8). TH-302, available for intravenous (IV) infusion, will be administered one week before start of chemoradiotherapy (d4), continued on a weekly basis for a total of 6 doses. TH-302 should be administered prior to Carboplatinum/paclictaxel and prior to radiotherapy. The administration of chemotherapy should start 2 to 4 hours after completion of the TH-302 infusion. During phase I, the initial dose level of TH-302 will be 120 mg/m2 with infusion over 30 to 60 minutes. The following dose escalations will be implemented: level 2 = 240 mg/m2 and level 3 = 340 mg/m2. In case of toxicity at the first dose level, inclusion in level -1 (60 mg/m2) is planned. Intermediate doses may be explored based on the cumulative safety data. In combination with the investigating drug, the standard regimen of chemotherapy will be administered: Paclitaxel (50 mg/m2) and Carboplatin (AUC = 2 mg/ml/min) will be given by intravenous infusion weekly for a total of 5 doses starting on the day 11. Chemotherapy will be combined with fractionated irradiation (RapidArc) to a total dose of 41.4Gy administered in 23 fractions of 1.8Gy 1, starting the first day of the first cycle of chemotherapy (shown in figure 1).

Study burden and risks

Patients participating in the trial will be subjected to a baseline HX4 PET/CT scan before the start of any treatment. One week before the start of the standard chemoradiotherapy, patients will receive the first intravenous administration of TH-302 on an out-patient base, followed by HX4 imaging four days later. The blood samples for the hypoxia biomarker expression will be collected on the same days as the HX4 scans. During the standard chemoradiotherapy treatment, TH-302 will be administered 2-4 hours prior to the chemotherapy (Carboplatinum/Paclitaxel) and no additional hospital visit is required. So in conclusion, we foresee three additional hospital visits (two at

MAASTRO Clinic and one at Atrium-Orbis Medical Center):
*Day 1 (Friday): Hx4 imaging (MAASTRO clinic)
*Day 4 (Monday): First dosage TH-302 IV (Atrium/Orbis)
*Day 8 (Friday): Hx4 imaging (MAASTRO clinic)
The potential benefit of this combined treatment is the overcoming of the resistance to chemoradiation in hypoxic tumor regions, by administration of the drug TH-302. TH-302 is expected to have little broad systemic toxicity due to its selective activation under hypoxic conditions. Prognosis of patients with esophageal cancer remains dismal, especially for non-responders to chemoradiotherapy (5-year overall survival varying from 10 to 30%). There is evidence that complete responders to chemoradiotherapy have better outcome, so every gain in treatment effect is worthwile.

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 esophagus
*Age>18 years
*UICC T2-4 N0-2 M0, potentially resectable disease
*Patient discussed at tumour board (multidisciplinary team meeting)
*No evident tumor invasion in nearby regions like aorta, trachea
*WHO performance status 0-2
*Less than 10 % weight loss the last 6 months
*Laboratory requirements within 7 days prior to enrollment (start chemoradiotherapy):
Haemotology: haemoglobin >10g/dl, absolute neutrophils * 1.5 x 109/L,platelets * 100x109/L
Biochemistry:bilirubin within normal limits, AST(SGOT)/ALT (SGPT) * 2.5 institutional upper limit, Creatinine clearance * 60 ml/min.
*Willing and able to comply with the study prescriptions
*No history of prior thoracic radiotherapy
*No severe chronic obstructive pulmonary disease with hypoxemia or in the opinion of the investigator any physiological state leading to hypoxemia
*Women should not be pregnant or lactating
*No known infection with HIV, hepatitis B or C or any other active infection
*Normal ECG with careful evaluation of QT/QTc
*Have given written informed consent before patient registration

Exclusion criteria

*Recent (< 3 months) severe cardiac disease (arrhythmia, congestive heart failure, infarction)
*Patients with difficult peripheral intravenous access
*History of prior thoracic radiotherapy
*Severe chronic obstructive pulmonary disease with hypoxemia or in the opinion of the investigator any physiological state leading to hypoxemia
*Women who are pregnant or lactating
*Known infection with HIV, hepatitis B or C or any other active infection

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	18
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	TH-302
Generic name:	TH-302

Ethics review

Approved WMO

Date:	01-07-2015
Application type:	First submission
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)

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
Other	14-27-03/09

Register	ID
EudraCT	EUCTR2014-004700-30-NL
CCMO	NL52134.096.15