Integration of Trastuzumab, with or without Pertuzumab, into Perioperative Chemotherapy of HER2-Positive Stomach Cancer: The INNOVATION Trial (EORTC-1203-GITCG)

**Condition**
Resectable, HER2-positive gastric or gastroesophageal junction adenocarcinoma (UICC stage Ib–III)

**ClinicalTrials.gov Identifier**
NCT02205047

**EudraCT Number**
2014–000722–38

**Study Design**

- **Study Type:** Interventional
- **Study Phase:** II
- **Allocation:** Randomized
- **Intervention Model:** Three-Arm Assignment
- **Masking:** Open-Labelled
- **Primary Purpose:** Treatment
- **Estimated Enrollment:** 225 Patients

**Interventions**

- **Study Arm A (control group):** Cisplatin (80 mg/m² every 3 weeks) and capecitabine (1000 mg/m² twice daily every 2 out of 3 weeks), or 5-FU (800 mg/m²/day for 5 days every 3 weeks) for 3 cycles of 3 weeks before and after surgery.

- **Study Arm B:** Chemotherapy as in the control group, plus trastuzumab (8 mg/kg loading dose, followed by 6 mg/kg every 3 weeks) at day 1 of every chemotherapy cycle, but continued after the end of chemotherapy for a total of 17 cycles.

- **Study Arm C:** Chemotherapy plus trastuzumab as in experimental arm 1, plus pertuzumab (840 mg every 3 weeks) at day 1 of every chemotherapy and trastuzumab cycle, continued after the end of chemotherapy for a total of 17 cycles in combination with trastuzumab.

**Primary Outcome Measure**
Major pathological response rate (<10% vital residual tumor cells) according to Becker et al., as determined by independent review of 2 blinded expert pathologists.

**Sponsor**
European Organisation for Research and Treatment of Cancer, Bruxelles

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**Description**

This international, randomized phase II trial is a collaboration between EORTC (leading group), the Korean Cancer Study Group, who committed to recruit 50% of the patients, and the Dutch Upper GI Cancer Group. It has been designed to assess the impact of integrating trastuzumab alone and the combination of trastuzumab and pertuzumab in the perioperative treatment of resectable, HER-2 positive adenocarcinoma of the stomach, on the major pathologic response rate (primary endpoint). The treatment schedule (e.g. total duration of the antibody treatment) has been adapted from the experience in breast cancer.

The randomization will be 1:2:2 (control : experimental arm 1 : experimental arm 2). Potentially eligible patients will be screened centrally for the HER2 status. After confirmation of HER2-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 3 treatment arms. Stratification will be done by histological subtype (intestinal/non-intestinal); Korea versus Europe; stage II versus III; node-positive versus node-negative. After analysis of the primary endpoint the advice of the EORTC Independent Data Monitoring Committee will be sought regarding the possible conduct of a phase III trial. With an expected recruitment of 4 years, and 6 years of follow-up after surgery, the total study duration will be approximately 10 years.

Eligibility Criteria

Inclusion Criteria

- Ages eligible for study: 18 years and older
- Genders eligible for study: both
- Histologically proven, gastric or gastroesophageal (GE)-junction adenocarcinoma (Siewert I–III)
- Patient medically fit for gastrectomy/oesophagogastrectomy as decided by the investigator
- WHO performance status 0–1
- HER2 overexpression
- Amenable to gastrectomy/oesophagectomy
- The cardiac ejection fraction (LVEF), as determined by echocardiography, multiple gated acquisition scan (MUGA) or cardiac MRI should be at least 50%
- Adequate organ function
- Written informed consent
- For women who are not postmenopausal (>12 months of non-therapy 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 the treatment period and for at least 12 months after the last treatment dose
- For men: agreement to remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period and for at least 12 months after the last dose of study treatment. Abstinence is only acceptable if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g. calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods for contraception

Exclusion Criteria

- Absence of distant metastases on CT scan of thorax and abdomen
- Prior chemo- or antibody therapy
- History of significant cardiac disease
- Current uncontrolled hypertension
- Known hypersensitivity to the components of trastuzumab, pertuzumab, cisplatin, 5-FU or capecitabine
- Known dihydropyrimidine dehydrogenase (DPD) deficiency
- Ongoing or concomitant use of the antiviral drug sorivudine or its chemically related analogs, such as brivudine
- Chronic treatment with high-dose intravenous corticosteroids
- 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.
- Psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule
- Pregnant or breast feeding
Why this Trial Is Important to Me

The Trastuzumab for Gastric Cancer (ToGA) study that was published in 2010 proved that the monoclonal HER2-antibody trastuzumab given in addition to cisplatin-fluoropyrimidine first-line chemotherapy significantly prolongs survival in patients with HER2-positive advanced gastric cancer (GC) [1]. This major advance led to the regulatory approval of trastuzumab for first-line treatment of HER2-positive advanced GC in most parts of the world.

Careful investigation of HER2 expression preceded ToGA and contributed to establish HER2 as a relatively robust predictive biomarker for trastuzumab efficacy [2]. Specific expression patterns of HER2 in GC, especially its extensive intratumoral heterogeneity, make this target more difficult to assess compared with breast cancer [3]. Sampling errors leading to false-negative or false-positive results can occur even in experienced laboratories [4].

While the role of anti-HER2 targeted trastuzumab for advanced GC is well established, its value is yet undetermined in the perioperative setting. 2 single-arm phase II studies assessed the feasibility of neoadjuvant chemotherapy with trastuzumab [5, 6]. The investigators reported interesting complete response rates up to 22% which raise hope that survival rates may also improve. This hypothesis needs to be confirmed by prospective randomized trials. The European Organisation of Research and Treatment of Cancer (EORTC) INNOVATION study randomly allocates patients with stages Ib–III GC to receive neoadjuvant chemotherapy alone or chemotherapy plus trastuzumab or chemotherapy plus trastuzumab and pertuzumab (NCT02205047). INNOVATION was designed to prove the value of anti-HER2 directed therapy for patients with localized HER2-positive GC.

INNOVATION has a well elaborated quality assurance program. A strong focus is put on biomarker assessment that will be done centrally in highly experienced laboratories. Tumor and plasma sampling will allow for correlative research that may lead to better understanding HER2-resistance mechanisms in subsets of GC patients. We also plan to implement metabolic imaging using sequential 18F-FDG PET in selected centers. This approach has shown high potential to discriminate responders from non-responders to neoadjuvant chemotherapy early on [7].

INNOVATION is an excellent example of international scientific collaboration. Besides the traditional EORTC centers we acquired a new strong partnership with centers located in central Europe and in the Baltic states. We also managed to associate the Dutch Upper Gastrointestinal Cancer (DUCG) study group and the Korean Gastric Cancer Study Group (KGCSG), making INNOVATION an important global, investigator-driven, academic clinical network study.

References


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