**FULL PROTOCOL TITLE**

# TOPGEAR: Trial of Preoperative Therapy for Gastric and Esophagogastric Junction Adenocarcinoma. A randomised phase II/III trial of preoperative chemoradiotherapy versus preoperative chemotherapy for resectable gastric cancer

**STUDY CHAIRS**

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**LINK TO STUDY**

https://gicancer.org.au/clinical-trial/topgear/

**TRIAL IDENTIFIER**

ACTRN12609000035224

**COORDINATING CENTRE**

NHMRC Clinical Trials Centre

**FUNDING SOURCES**

NHMRC Clinical Trial and Cohort Studies Grant

## STUDY CHAIR

### Prof Trevor Leong

Peter MacCallum Cancer Centre

**FINANCIAL DISCLOSURE**
None to declare.

## AIM/S

The primary objective is to investigate whether preoperative chemoradiotherapy is superior to preoperative chemotherapy alone in patients undergoing adequate surgery (D1+ dissection) for resectable gastric cancer.

## BACKGROUND

Gastric cancer remains a significant global public health problem. Although in developed countries its incidence has dramatically decreased, on a worldwide scale it is still a leading cause of cancer related deaths. Surgery is the only potentially curative treatment for gastric cancer.

Although the survival rates for patients with early stage disease (stage 1A and 1B) are good, this subgroup of patients constitutes only 20% of those undergoing resection. The majority of patients will have locally advanced or metastatic disease at presentation, which has an extremely poor prognosis. The current five-year survival rate for gastric cancer in Western countries is approximately 20%, a figure that has improved little over the past 30 years. Despite this rather grim outlook, there have been several important advances utilising chemotherapy and radiotherapy in the adjuvant setting that have generated renewed interest and debate in the treatment of resectable gastric cancer.

Since the publication of the INT0116, MAGIC and CRITICS trials, the role of radiotherapy in the treatment of gastric cancer has become uncertain  The important question that needs to be addressed is whether chemoradiotherapy is superior to chemotherapy alone in the neoadjuvant treatment of resectable gastric cancer.

## STUDY DESIGN

This is an international, intergroup trial led by investigators from the AGITG and the NHMRC Clinical Trials Centre, in collaboration with the Trans-Tasman Radiation Oncology Group (TROG), the European Organisation for Research and Treatment of Cancer (EORTC) and the Canadian Cancer Trials Group (CCTG).

TOPGEAR is a multicentre, prospective, randomised, stratified, phase II/III clinical trial. Eligible participants will be randomly allocated to either preoperative chemotherapy or preoperative chemoradiotherapy. The trial has been conducted in two parts. Part 1 was the phase II component of the trial that recruited 120 participants, while Part II is the phase III component that recruited a further 450 participants to provide a total sample size of 570 patients.

## ELIGIBILITY CRITERIA

Adults (18+ years) with historically proven adenocarcinoma of the stomach or gastroesophageal junction that is:

a. Stage IB (T1N1 only) to IIIC, i.e. T3-T4 and/or N +ve,
b. Considered operable following initial staging investigations.

## STUDY UPDATE

The study opened to recruitment in September 2009 and reached its phase II recruitment milestone of 120 patients on 24 June 2014. TOPGEAR then reached its final accrual target in May 2021, with 574 participants recruited (244 from ANZ, 157 from Canada, and 173 from Europe) from 70 sites across 15 countries. Early safety data as well as Radiotherapy Quality Assurance results have been published. The main outcome data will be analysed soon.

All participants have completed study treatment and are now in follow-up.

## TRANSLATIONAL RESEARCH

Pre- and post-treatment tissue samples are collected (fresh and/or snap frozen and/or FFPE) where possible. Serial blood samples are collected pre-treatment, during treatment and at regular intervals during follow-up, ideally until recurrence from consenting participants. These samples are planned to be used to address some important translational research questions such as:

- Are there biomarker and biological determinants of chemotherapeutic and radiotherapeutic response in gastric cancer?
- Are there biological differences in remnant disease that differs from the primary lesion and could be useful to target specific therapeutics?

A translational research sub-study is led by Prof Alex Boussioutas.

## STUDY SCHEMA

### Eligibility

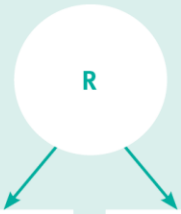
Adults ≥18 years with histologically proven adenocarcinoma of the stomach or gastroesophageal junction that is:

a. Stage IB (T1N1 only) – IIIC, i.e. T3 – T4 and/or N +ve,
b. Considered operable following initial staging investigations

### Stratification

- Age: <50yrs vs 50yrs – 70yrs vs >70yrs
- Primary tumour site: gastroesophageal junction (esophago-gastrectomy [Ivor-Lewis]) vs gastroesophageal junction (total gastrectomy) vs upper third vs middle third vs lower third vs tumour extends into 2 or more of the above adjacent sites
- Clinicial tumour stage: T1-2 vs T3-4
- Clinical nodal stage: N+ve vs N-ve
- Gender
- Site/Institution
- PET
- EUS
- Laparoscopy
- Chemotherapy regimen

*Duration of accrual: 10 years*
*Duration of follow-up: up to 5 years*




**Group 1 (Control Arm)**
ECF (or ECX) or EOX) x 3
Repeated every 21 days
OR
FLOT x 4
Repeated every 14 days
+
SURGERY (D1+)
+
ECF (or ECX) or EOX) x 3
Repeated every 21 days
OR
FLOT x 4
Repeated every 14 days

**Group 2**
ECF (or ECX) or EOX) x 2
Repeated every 21 days
OR
FLOT x 3
Repeated every 14 days
+
PREOP CRT
45 Gy + Cl 5-FU (or X)
+
SURGERY (D1+)
+
ECF (or ECX) or EOX) x 3
Repeated every 21 days
OR
FLOT x 4
Repeated every 14 days

### Endpoints

**Primary endpoint**
Overall survival
Safety

**Secondary endpoints**
Disease free survival
Pathologic response rate
Treatment administration