Efficacy and Safety of Folfirinox as Neoadjuvant Chemotherapy for Resectable Gastric or Gastroesophageal junction adenocarcinoma- a run- in pilot followed by Phase 2 comparison between ECF and FOLFIRINOX – FIG study

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INVESTIGATORS STATEMENT

I, ……………………………………………………………. THE UNDERSIGNED, UNDERSTAND THAT THE STUDY WILL NOT BE STARTED WITHOUT PRIOR WRITTEN APPROVAL OF THE Human Research Ethics Committee. No changes will be made to the study protocol without the prior written approval of the Sponsor and the Research Ethics Committee.

I have read, understood, and agree to abide by all the conditions and instructions contained in this protocol. I agree to comply with the ICH Harmonized Tripartite Guideline for Good Clinical Practice for conducting clinical trials and local regulations and will conduct thee above study under these standards.

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Principal Investigator Date

**Background**

Gastric cancer (GC) is the fourth most common cancer globally, and the second leading cause of cancer death. With an annual global incidence of more than 952,000 cases of gastric cancer (GC) and 456,000 cases of esophageal cancer (EC), upper GI (UGI) malignancies are major worldwide cancer risks.

Over the past 30 years in the West, the incidence trends of GC and EC, including gastroesophageal junction (GEJ) adenocarcinomas, have been trending in opposite directions. In the United States, predictions for 2015 call for 18,170 new cases of EC, with 15,450 deaths, and 22,220 new cases of GC, with 10,990 deaths.

Complete surgical resection of GC remains the cornerstone of curative treatment.  The outcome among these patients is determined by the stage of the disease at presentation.

In population-based series of Western populations, the five-year survival rate for patients with completely resected stage I gastric cancer is approximately 70 to 75 percent, while it drops to 35 percent or less for stage II disease and beyond. Efforts to improve cure rates have included preoperative (neoadjuvant), perioperative, and postoperative therapies.

The largest study supporting perioperative chemotherapy is the MAGIC phase III trial, which randomly assigned a total of 503 patients with stage II or III GC or GEJ tumors (74% and 26%, respectively) to three cycles of chemotherapy with cisplatin, epirubicin, and continuous-infusion FU before and after surgery or surgery alone. Postoperative complications were similar in the two arms. OS and progression-free survival were significantly improved with the addition of perioperative chemotherapy, with 5-year survival increased from 23% to 36%. Although 86% of patients assigned to perioperative chemotherapy completed all planned preoperative chemotherapy, only 42% of patients completed both preoperative and postoperative systemic therapies. Patients undergoing surgery were 92% and curative resection was achieved in 64%. Greater proportion of T1 and T2 tumors (51 vs 36%) and N0 and N1 (84 vs 70%) were noted in the pre-operative chemotherapy arm as compared to surgery alone. The French FFCD (Federation Francophone de Cancerologie Digestive) 9703 trial also reported benefit from perioperative chemotherapy, with 5-year OS improvement from 24% to 38% in favour of perioperative chemotherapy. As in the MAGIC study, the majority of patients completed preoperative treatment (87%), whereas fewer than half (48%) received the postoperative component. In a study by Vallbo¨hmer et al 42 patients were treated with neoadjuvant chemo followed by curative resection in 88%. A >50% pathological response was seen in 15% and correlated with better survival. In another study looking at tumor regression and survival after preoperative ECF chemotherapy, pathological tumor response (any response) was noted in 35%.

A recent review of 14 randomized controlled trials with 2,422 patients with gastroesophageal adenocarcinoma found that preoperative chemotherapy conferred a longer OS (HR, 0.81; 95% CI, 0.73 to 0.89; P < .001) compared with surgery alone and was associated with longer disease-free survival, higher likelihood of R0 resection, and increased tumor downstaging without increased perioperative complications.

Results from completed perioperative trials do not suggest a best systemic combination therapy. Although fluoropyrimidine and platinum combinations have been the most tested, the contribution of adding an anthracycline or taxane has not been adequately addressed and is being evaluated in an ongoing Dutch study. Oxaliplatin and irinotecan have shown better efficacy and tolerability than the standard ECF regimen in advanced/ metastatic gastric cancer. In a phase III trial, Epirubicin, Oxaliplatin and FU (EOX) was found to be superior in terms of efficacy and tolerability against ECF. In another phase II randomised trial irinotecan was equally effective but better tolerated than ECF regimen.

Capecitabine and Oxaliplatin has shown efficacy as adjuvant treatment post curative gastric resection in a large phase III randomised trial. In the CLASSIC trial, 1035 patients with stage II- IIIB gastric cancers were randomised (520 to receive chemotherapy and surgery, 515 surgery only). Adjuvant chemotherapy consisted of eight 3-week cycles of oral capecitabine (1000 mg/m(2) twice daily on days 1 to 14 of each cycle) plus intravenous oxaliplatin (130 mg/m(2) on day 1 of each cycle). 3 year disease-free survival was 74% (95% CI 69-79) in the chemotherapy and surgery group and 59% (53-64) in the surgery only group (hazard ratio 0·56, 95% CI 0·44-0·72; p<0·0001). Grade 3 or 4 adverse events were reported in 279 of 496 patients (56%) in the chemotherapy and surgery group and in 30 of 478 patients (6%) in the surgery only group. The most common adverse events in the intervention group were nausea (n=326), neutropenia (n=300), and decreased appetite (n=294).

Folfirinox has established itself as a standard of care in advanced pancreatic and colorectal cancer and is one of the standard first line treatment options in these two malignancies. The main side effects of this regimen has been myelosuppression with febrile neutropenia seen in 5.4 % and gr III, IV fatigue in 24% and diarrhea in 12%

Neoadjuvant FOLFIRINOX in the setting of borderline resectable pancreatic cancer has also shown encouraging results with more patients able to undergo an R0 resection with acceptable toxicity.

Recently a pooled analysis from two independent ongoing clinical trials from University of Chicago and Washington showed efficacy of FOLFIRINOX in first line metastatic setting of gastric cancer. ORR was 62.5% and mPFS was 8 months which are promising. The doses used in this study were standard and will be used in the current study.

This trial will assess whether Folfirinox can be used as neoadjuvant chemotherapy for gastric cancer.

**Aim**

To assess feasibility and efficacy of Folfirinox as Neoadjuvant Chemotherapy for patients undergoing curative resection for Gastric or Gastroesophageal junction adenocarcinoma

**Objective**

The present trial is designed to determine whether a regimen of Folfirinox given before radical surgery improves the outcomes of operable gastric or GEJ adenocarcinoma as compared to current standard ECF chemotherapy

The primary end point

1. Progression-free survival (PFS). Progression-free survival (PFS) is the time from the date of randomization to the date of event defined as the first documented progression or death due to any cause. If a patient has not had an event, PFS is censored at the date of last adequate tumor assessment.

Secondary end points

1. Ability of patients to proceed to curative gastric resection. The first 10 patients treated will form part of the pilot phase. Ability of 6 patients to undergo curative gastric resection within 18 weeks of starting FOLFIRINOX will allow the opening of the randomised phase II portion.

2. Feasibility of this regimen by assessing toxicities and side effects. Adverse drug reactions and serious adverse drug reactions will be assessed by CTCAE Version 4.0, changes in hematology and chemistry values, specifically those associated with hepatic and renal function; and assessment of physical examinations, vital signs and electrocardiograms

2. Pathological complete response including surgical assessments of down-staging (i.e., tumor diameter, tumor stage, and nodal status).

3. Overall survival (OS). This is defined as the time from histological diagnosis to date of death.

**Eligibility**

1. Patients >18 years age

2. Patients with cytological or histological confirmed gastric adenocarcinoma or gastroesophageal junction adenocarcinoma

3. Able to sign Informed Consent

4. World Health Organization (WHO) Performance Status of < 1

5. Localised gastric cancer or gastroesophageal junction adenocarcinoma considered for curative radical gastrectomy. Eligible patients will have ≥ T2 gastric cancer and/ or Siewert III GOJ cancer (cancer of the cardia)

6. Patients must have the following laboratory values:

Hematologic:

* Absolute Neutrophil Count (ANC) ≥1.5x109/L
* Hemoglobin (Hgb) ≥ 9 g/dl
* Platelets (plt) ≥100x109/L

Biochemistry:

* Potassium within normal limits
* Total calcium (corrected for serum albumin) and Phosphorus within normal limits
* Adequate liver function defined as:
* AST/SGOT and ALT/SGPT ≤ 1.5 x Upper Limit of Normal (ULN) if AP > 2.5 ULN
* Serum bilirubin ≤ 1.5 x ULN
* Adequate Kidney function test : Serum creatinine ≤ 1.5 x ULN or creatinine clearance ≥ 50 ml/min on standard Cockcroft-Gault Equation

**Study design and treatment schedule**

First 10 patients treated will form the pilot phase of the trial. Once the feasibility of the regimen is confirmed, the phase II randomised portion will be opened where patients will be randomised in 1:1 ratio to standard ECF chemotherapy versus FOLFIRINOX. The feasibility will be defined as the ability of 6 out of 10 pilot patients to undergo curative gastric resection within 18 weeks of starting FOLFIRINOX

Patients will be adequately staged using CT scan chest/ abdomen/ pelvis, Echo, lung functions and laparoscopy to rule out metastatic disease and assess fitness for curative gastric resection. The patients will be discussed at the Statewide Upper GI MDT.

Patients will be consented and have PICC or PORT inserted prior to start of treatment.

Folfirinox Chemotherapy will be administered for six cycles preoperatively (3 months).

A typical cycle will consist of oxaliplatin 85 mg/m2; irinotecan 150 mg/m2; leucovorin 50mg; and FU 2400 mg/m2 46-hour continuous infusion, once every 2 weeks. Patients will be provided with adequate anti emetics and supportive medications as per the institution preference. Growth factors and prophylactic antibiotics are not mandated.

ECF chemotherapy will be given as per the standard doses and schedule with 3 cycles pre-op and 3 cycles post operatively. Before each cycle of chemotherapy, a complete blood count, renal and liver function tests will be checked. Patients will be reviewed and assessed every two weeks in the FOLFIRINOX arm and every 3 weeks in the ECF arm prior to each chemotherapy cycle.

After completing all prescribed cycles of chemotherapy, patients will undergo restaging with CT scan and endoscopy prior to surgery. A minimum interval of 3 weeks will be mandated from last day of chemotherapy to surgery. Majority of the patients will have surgical resection within 3-6 weeks of completing chemotherapy. Post surgery, patients will be followed clinically every 3 months and will have surveillance CT scan at 3, 6, 12, 24 and 36 months or as clinically indicated.

**Blood and tissue collection and storage**

**Biomarker Evaluation**

The diagnostic biopsy and surgical resection undertaken for patients prior to the commencement of trial treatment provide an invaluable opportunity to obtain tumour tissue that may be analysed for biological markers in cancer. Blood samples for research will also be collected during the screening period and at the time of routine pre-treatment blood tests.

Patients will be asked for an optional consent to unspecified future laboratory research on their tissue and blood samples as well as linkage of these to their health information. This optional consent will not affect patients’ participation in the main part of this trial. The information collected will not be used to identify any patient and the TMC will seek separate ethical approval for specific translational studies once individual study designs have been finalised.

The studies will include but not be limited to analyses of potential biomarkers of response to treatment, potential prognostic and predictive biomarkers and may involve but not be limited to techniques such as genome-wide association analysis, next generation sequencing, exome and transcriptome sequencing and ELISA assays.

**Tissue collection**

Tissue samples from the time of diagnostic biopsy and surgical resection are routinely stored at pathology laboratories where initial histological assessments were performed. For patients who consent to an optional unspecified laboratory research, archived tissue samples will be accessed in future for further testing. As mentioned above patients will be asked as an optional consent for future access to their archived tumour tissue for future biomarker research. All future research proposals will be sent for separate ethics committee approval prior to any biomarker research.

**Central blood collection**

Blood will be obtained after the informed consent during the screening period and at the time of routine pre-treatment blood tests. These samples will be stored for future analyses. This blood collection is required for all study patients.

**Ethical considerations**

Written informed consent must be obtained from all patients before entering this study. Patients will be supplied with Patient Information Sheet. The study will be submitted to respective Hospital Ethics Committee for approval before patients can be entered into the study. Participation into this study is voluntary. Patients will be made aware that their decision not to take part or to withdraw from the study has no influence on routine treatment, their relationship with treating physicians or treating centres through Patient Information Sheet.

**Confidentiality**

The study will be conducted in accordance with applicable Privacy Acts and Regulations. All data generated in this study will remain confidential. All information will be stored securely in clinical data base of the Oncology Clinical Trials Unit, Royal Adelaide Hospital and will only be available to staff directly involved with the study.

**Statistical Analysis**

The ability of 6 patients to undergo curative gastric resection within 18 weeks of starting FOLFIRINOX will allow opening of the randomised phase II portion of the trial.

The PFS in the ECF arm was 45% at 2 years. A clinically meaningful improvement would be increase to 65% in the experimental arm at 2 years.

Group sample sizes of 96 in Group 1 and 96 in Group 2 achieve 80% power to detect a difference between the group proportions of 0.200. The proportion in Group 1 (the treatment group) is assumed to be 0.4500 under the null hypothesis and 0.6500 under the alternative hypothesis. The proportion in Group 2 (the control group) is 0.4500. The test statistic used is the two-sided Z test with pooled variance. The significance level of the test was targeted at 0.0500. To compare two survival proportions at the end of 2 years, Z test if fine and the sample size calculation is actually based on Z test with pooled variance, not Person chi-square test.

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**Dataset for the Pathological Reporting of**

**Gastric Carcinoma**

**MACROSCOPIC FINDINGS**

**Type of specimen**

□ Partial gastrectomy

□ proximal

□ distal

□ Total gastrectomy

□ Local resection

□ Other (specify)……………………….

**Specimen dimensions**

Length of stomach: greater curve \_\_\_\_\_\_\_\_\_mm

Length of stomach: lesser curve \_\_\_\_\_\_\_\_\_mm

Length of oesophagus: \_\_\_\_\_\_\_\_\_mm

Length of duodenum: \_\_\_\_\_\_\_\_\_mm

**Site of tumour**

□ Cardia

□ Fundus

□ Body

□ Antrum

□ Other (specify) \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Maximum tumour diameter: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**mm

**Distance of tumour to nearest margin: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**mm

**Configuration of tumour**

□ Polypoid, ulcerating or fungating

□ Diffusely infiltrating

**MICROSCOPIC FINDINGS**

□ Adenocarcinoma

□ Other (specify) \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

# Lauren classification

□ Intestinal

□ Diffuse/mixed

**Assessment of Grade** (highest grade in any part of the tumour)

□ Well/moderately differentiated

□ Poorly differentiated

**Local invasion**

□ T0 No tumour identified

□ Tis Carcinoma *in situ:* intraepithelial tumour without invasion of lamina

propria

□ T1 Invasion of lamina propria/submucosa

□ T2a Invasion of muscularis propria

□ T2b Invasion into subserosa

□ T3 Invasion of serosa (visceral peritoneum) without invasion of adjacent

structures

□ T4 Invasion of adjacent structures

**Proximal margin involved:**

□ Yes

□ No

**Distal margin involved:**

□ Yes

□ No

**Circumferential margin lower oesophagus:** Involvement (< 1 mm):

□ Yes

□ No

□ N/A

If no, distance of tumour to nearest circumferential margin: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_mm)

**Lymphatic/vascular invasion**

□ Yes

□ No

**Lymph nodes:**

*(all specimen nodes will be examined)*

□ N0 (0 nodes)

□ N1 (1–6 nodes)

□ N2 (7–15 nodes)

□ N3 (>15 nodes)

Number examined: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Number positive: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Distant metastases**

□ No (M0)

□ Yes (M1)

□ Unknown/cannot be assessed (MX)

**Completeness of resection**

□ R0 - all margins clear

□ R1 - macroscopically clear resection but microscopically positive margin(s)

□ R2 - macroscopically positive margin(s)

**PATHOLOGICAL STAGING**

**(y) pT\_\_\_ pN\_\_\_ pM\_\_\_** (TNM 5th edition)

**(y) pT\_\_\_ pN\_\_\_ (i+/-) pM\_\_\_** (TNM 6th edition)

(“y” post neoadjuvant therapy, “i” – isolated tumour cells)