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PRODIGE
PARTENARIAT DE RECHERCHE EN ONCOLOGIE DIGESTIVE

PRODIGE 58 – UCGI 35 – REGIRI

REGorafenib combined with IRInotecan as second-line treatment in patients with metastatic gastro-oesophageal adenocarcinomas: A randomized phase II trial

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Background

Gastric cancer (GC) is an aggressive malignancy and the 3rd cause of all cancer deaths worldwide. The median OS for patients with recurrent or metastatic GC remains lower than 1 year and the pooled analysis of REGARD and RAINBOW data showed a median OS of 6.9 months for patients in 2nd line settings (Fuchs CS *et al.* J Gastric Cancer 2017).

Several options have been evaluated and are recommended as **second-line treatment in metastatic gastroesophageal adenocarcinomas** (MGA) after failure of first line 5FU and cisplatin based chemotherapy: docetaxel, paclitaxel, and irinotecan as monotherapies or paclitaxel combined with ramucirumab.

Regorafenib monotherapy showed promising efficacy data as 2nd or 3rd line MGA (INTEGRATE trial; Pavlakis N *et al*, J Clin Oncol. 2016). The aim of REGIRI study is **to evaluate the efficacy of regorafenib combined with irinotecan compared to irinotecan alone.**

Study design

REGIRI is a multicenter, phase 2, open-label randomised study (NCT03722108).

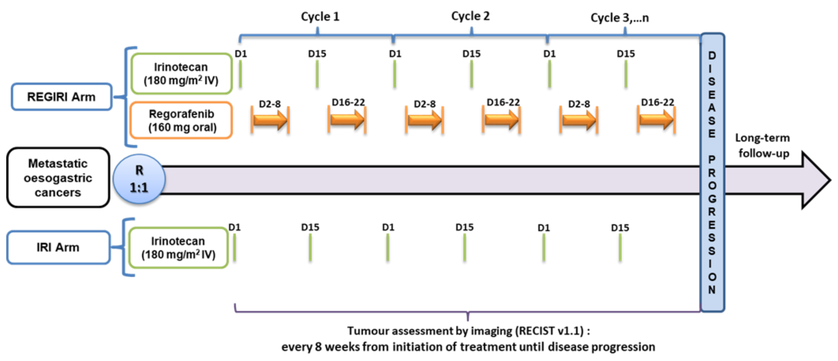

Figure 1 - REGIRI study design

Randomisation 1:1 stratified on :

- Prior use of PD1/PD-L1 inhibitors
- Location of tumour (gastroesophageal junction vs. gastric adenocarcinomas)

Sample size : 154 patients, 122 events

Based on assumptions of OS from 6 months (IRI arm) to 10 months (REGIRI arm), HR=0,60, a-risk 5%, power: 80%, drop-out rate of 10%

Interim analyses:

- Safety interim analysis planned after 38 first patients enrolled in the experimental arm with predefined stopping rules based on the G3-4 diarrhoea rate
- Efficacy interim analysis planned after 40 OS events using the O'Brien-Fleming boundaries.

Objectives

Primary objective :

- To evaluate efficacy between the 2 treatment arms in terms of **Overall Survival**

Secondary objectives :

- To compare **efficacy** between the 2 treatment arms in terms of OS rate at 6 and 12 months, PFS, PFS rate at 6 and 12 monts, DCR, ORR
- **Safety** (NCI CTCAE v5.0)
- **Quality of life** (EORTC QLQ-C30 and OG25)

Ancillary objectives :

- **Pharmacokinetic** of regorafenib, irinotecan and metabolites
- **Pharmacogenetics**: cyclin D1 polymorphism
- Identifiaction of **tumour factors predictive of response** to REGIRI combination using IHC

Study treatment

Study treatment:

Patients will be treated until disease progression, unacceptable toxicity or patient withdrawal:

Control arm (IRI): Irinotecan 180 mg/m², IV infusion over 90 min on D1 and D15 of a 4-week cycle;

Experimental arm (REGIRI):

- Irinotecan 180 mg/m², IV infusion over 90 min on D1 and D15 of a 4-week cycle;
- Regorafenib 160 mg/day, per os, on D2-D8 and D16-D22 of a 4-week cycle

Justification for the therapeutic regimen:

Combination FOLFIRI + regorafenib previously evaluated in metastatic colorectal cancer (Schultheiss *et al*, 2013 & Sanoff *et al*, 2018)

- Same dose regimen: FOLFIRI including irinotecan 180 mg/m² every 2 weeks and regorafenib 160 mg/day 1 week on/1 week off
- Acceptable tolerance of the combination

Study Population

Main inclusion criteria:

- Patients ≥ 18 year of age
- Histologically proven gastroesophageal adenocarcinomas (gastric location or gastroesophageal junction Siewert II and III),
- Asymptomatic primary tumour,
- Metastatic disease,
- Disease progression after a fluoropyrimidine and platinum based chemotherapy
- Performance status ECOG 0-1
- Normal hematologic, hepatic, renal and other vital functions
- Measurable lesions (RECIST 1.1 criteria)
- Signed informed consent

Main non-inclusion criteria:

- Symptomatic brain metastases or carcinomatous meningitis
- Bone-only metastases
- UGT1A1 deficiency
- Gilbert syndrome
- Another cancer within 5 years prior to randomisation, except for in situ cervical cancer, non-melanoma skin cancer and superficial bladder tumours
- Major comorbidity (HIV, active or chronic HBV or HCV, cardiac disorders)
- Any other contra-indication to regorafenib and irinotecan

Study Status

Study timelines

- Start of recruitment in Feb 2019
- Planned end of recruitment in March 2022
- Primary endpoint analysis expected in **December 2022**

Accrual status

As of June 20th, 2019, **6 patients were randomized** out of **154 planned patients** (figure 3).

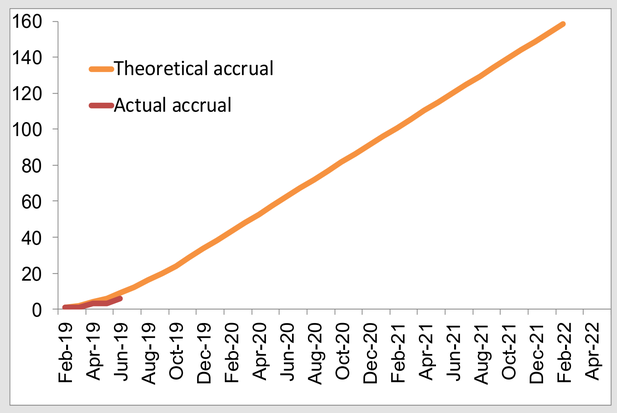

Figure 2 - Accrual status

Investigator sites

Figure 3 - Participating sites

Acknowledgment

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