SURGIGAST trial : Role of surgery in metastatic gastric adenocarcinoma v 21.02.2014

TITLE OF STUDY	Overall survival after palliative gastric resection plus chemotherapy versus chemotherapy only in stage IV gastric cancer
COORDINATING INVESTIGATOR	Pr. Christophe MARIETTE Department of Digestive and Oncological Surgery University Hospital C. Huriez Place de Verdun 59037 Lille Cedex France Tel: +333 20 44 44 07 - Fax: +333 20 44 43 85 Email : christophe.mariette@chru-lille.fr
CO-COORDINATOR	Dr Frédéric DI FIORE Department of medical oncology Centre Henri Becquerel Rue d'Amiens 76038 Rouen Cedex 1 Tel : 02 32 08 22 41 Email : Frederic.di-fiore@chu-rouen.fr
METHODOLOGISTS	Dr Andrew KRAMAR Department of biostatistics Centre Oscar Lambret, 3 rue Frédéric Combemale 59000 Lille Tel : 03 20 29 59 59 Email : a-kramar@o-lambret.fr Pr Alain DUHAMEL Department of biostatistics University Hospital of Lille, Place de Verdun 59037 Lille Cedex France Tel : 03 20 44 59 62 Email : alain.duhamel@univ-lille2.fr
PROMOTION	Lille University Hospital
SCIENTIFIC SUPPORTS	FRENCH (French Federation of Surgical Research) FFCD (French Federation of Digestive Oncology) UNICANCER PRODIGE (Partenariat de Recherche en Oncologie Digestive)
CONDITION	Patients with histologically confirmed adenocarcinoma of the stomach, locally resectable tumour and evidence of distant metastases (stage IV)
PRIMARY OBJECTIVE	To compare overall survival in patients with metastatic gastric cancer with and without resection of the primary tumour.
SECONDARY OBJECTIVES	- Quality of Life - Progression free survival - Surgical related postoperative morbidity - Chemotherapy related toxicities - Overall duration of hospitalization - Number of interventional palliative procedures
STUDY CONDUCT	After initial screening for eligibility by standard preoperative work up (diagnostic laparoscopy can be done but is not mandatory since being not the standard approach in metastatic disease), patients will benefit from 2 months of chemotherapy, according to local standards and national guidelines (www.tncd.org). Only patients without progressive disease according to the RECIST criteria will be eligible for randomisation into the study. Randomisation will be done 1 to 3 weeks after the end of initial chemotherapy between: Experimental intervention : Patients who are assigned to the surgical treatment group will undergo gastrectomy between D1 and D30 after randomization either subtotal or total gastrectomy, depending on the location of the primary tumour,

	except in case of distant peritoneal carcinomatosis (patients with peri-gastric and/or epiploic localized carcinomatosis should be resected) Standardized D2-lymphadenectomy is not required. Resection of metastasis is not required. Enteral nutritional support is strongly encouraged Chemotherapy should be started between 3 and 6 weeks postoperatively, with the same regimen as in the preoperative setting; alternative chemotherapy regimen might be discussed, according to local standards and national guidelines, in case of poor tolerance or pathological tumoral progression (www.tncd.org). <u>Control intervention :</u> Patients assigned to the conservative treatment group will continue the same chemotherapy regimen right after randomization. In both groups, <u>clinical re-evaluation</u> will take place after 6-8 weeks of post-randomisation chemotherapy, depending on the protocol used. Chemotherapy will be discontinued if the attending oncologist considers further chemotherapeutical treatment as non-beneficial for the patient; second line treatment is at the discretion of the medical oncologist participation in the trial. <u>Follow-up per patient :</u> Follow up will be provided every 3 months the first 2 years and according to local standards thereafter, until death. <u>Duration of intervention per patient :</u> Palliative chemotherapy will be continued as long as it is deemed beneficial to the patient. <u>Chemotherapy schemes allowed</u>: all those recommended in the French National Guidelines www.tncd.org
NCLUSION AND NON INCLUSION CRITERIA	<u>Inclusion criteria :</u> - Primary diagnosis of UICC stage IV gastric adenocarcinoma, histologically proven - Without any form of previous treatment (surgery and / or chemotherapy) for this diagnosis other than local endoscopic treatment - Histological proof of adenocarcinoma - Locally resectable primary tumour - ASA score 1 or 2 evaluated by the anaesthesiologist - Only one solid organ metastatic site (hepatic, lung, adrenal gland, bone, brain...). Patients with more than one metastasis in only one organ are eligible. - Age ≥ 18 years and ≤75 years - Adequate cardiac, respiratory, bone marrow, renal and liver function - Completion of baseline quality of life questionnaire (EORTC QLQC30 and STO 22) <u>Non inclusion criteria :</u> - Other histological subtype - ASA score 3, 4 or 5 - Diffuse peritoneal carcinomatosis diagnosed on preoperative work up - Metastatic disease involving more than one solid organ metastatic site on preoperative work up - Primary tumor irresectability or need for multivisceral resection with expected higher complication rate - Contraindication to chemotherapy or surgery according to the MDT decision - Second uncontrolled malignant tumour - Proximal tumour growth across the Z-line requiring abdomino thoracic or trans hiatal esophageal resection

	- Emergency surgery due to bleeding or perforation - Age > 75 years - Weight loss ≥ 20% persisting despite nutritional assistance
STUDY ENDPOINTS	<u>Primary efficacy endpoint :</u> Overall survival: the overall survival will be calculated from the date of randomisation and an event registered on the date of death of any cause. Patients lost to follow up or those with no death recorded on the day the database is frozen will be censored on the date of last follow up. <u>Key secondary endpoints:</u> - Quality of life (EORTC QLQC30 and STO 22 questionnaires) - Progression free survival, calculated from randomisation to progression accord to RECIST or death of any cause - Surgical related postoperative morbidity: grade III, IV and V complications according to the Dindo-Clavien classification, captured up to 90 days - Chemotherapy related toxicities: grade III, IV and V toxicities evaluated by NCI-CTCv4.0 - Overall cumulative duration of hospitalisation - Number of interventional palliative procedures per patient
STUDY TYPE	This is a multicentre prospective phase III open-labelled, two-armed, randomized controlled trial designed to prove superiority of the experimental treatment arm (surgery plus chemotherapy).
STATISTICAL ANALYSIS	Eligible patients will be randomised in a 1:1 fashion. The main endpoint is overall survival. From a weighted average of published studies, we expect a 45% 1-year survival rate in the control group (Mariette Ann Surg Oncol 2013, Mahar Gastric Cancer 2012, Chen Surg Oncol 2012, Wagner Cochrane 2010, Bouche J Clin Oncol 2004). With an expected 3-year accrual period, a minimum two-year follow-up period, two-sided type I error 0.05, and two interim analyses, a total of 376 deaths will provide 80% power to detect a 10% increase in the 1-year survival rate corresponding to a hazard ratio equal to 0.75. Two interim analyses are planned after the observation of one-third, and one-half of the expected number of deaths or at 124 and 188 deaths. Stratification will be done by minimization according to HER2 status, tumor location, ASA score, SRC histology, centre.
SAMPLE SIZE	Approximately 30% of patients will be dropped out after randomization due to distant peritoneal carcinomatosis at time of surgery (not visible on preoperative work up) and/or per-operative discovery of multiple metastatic sites. Based on previous hypotheses, the total number of subjects to be randomized is 424, 212 per arm.
TRIAL DURATION	Recruitment: 36 months Assess of the primary endpoint: 24 months after the last patient included Overall trial duration: 60 months
TRANSLATIONNAL STUDY	At initial screening and before initial chemotherapy administration, patients will benefit from a standard preoperative work up and eligible patients will be registered. Biopsies from the primary tumor will be stocked in tumor bank for assessing predictors of chemotherapy response. Comparison will be based on (i) RECIST criteria evaluation on CT scan for all patients before randomisation, (ii) histo-pathological response to chemo in the surgical arm. Additionally the prognostic role of the biomarkers will be assessed. All data will be available for being integrated in the national FREGAT clinico-biologic database, labelled by the INCa.
PARTICIPATING CENTERS	CHRU Lille (Pr Mariette) To be completed

FUNDING SOURCE	PHRC-K 2014
FINANCIAL ASPECTS	To be evaluated

SUMMARY

Due to the late onset of symptoms, gastric cancer is frequently diagnosed at an advanced stage and therefore in an incurable situation. A number of trials have reported an increase in overall survival and quality of life for palliative chemotherapy compared to best supportive care; data on surgical palliation, however, are scarce and generally do not take quality of life into account. Palliative therapy of any type of cancer firstly aims at preserving or re-establishing a good quality f life, which in the case of gastric cancer is impaired by the inability to eat or drink. Theoretically, the ideal treatment in this situation would be surgical resection of the primary tumour in order to (i) enhance survival, (ii) prevent perforation or bleeding and (iii) rapidly improve quality of life by removal of the stenosis. Taking into account the low complication rates of gastric surgery today, chemotherapy alone therefore may not be sufficient for state IV gastric cancer patients. This study is designed as a multicentre trial; patients with diagnosis of primary stage IV gastric adenocarcinoma who are willing to participate in the trial will be randomized to the surgical (gastric resection followed by chemotherapy) or the control (chemotherapy only) group. They will be asked to complete the EORTC QLQ C-30 and sto-22 questionnaires before intervention as well as during the 3-months basis follow up after randomisationt. Primary objective will be overall survival and secondary objectives will be quality of life, progression free survival, surgical related postoperative morbidity, chemotherapy related toxicities, overall duration of hospitalization and number of interventional palliative procedures .

KEY WORDS

Stage IV gastric cancer, palliative surgery, chemotherapy, quality of life, survival, randomised phase III trial.