A randomised controlled trial of neoadjuvant chemotherapy (NAC) and controlled D2 gastrectomy versus D2 gastrectomy alone for advanced gastric cancer resectable with curative intent: Ancillary study of the role of PET-scan for the early detection of responders to NAC

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**Aim:** The primary objective of this phase III trial is to compare OS of controlled D2 gastrectomy, with or without NAC, in patients with resectable GC. Secondary objectives are to compare the two arms for the proportion of patients undergoing D2 surgery, curative resection rate, perioperative complications and disease-free survival (DFS), to assess toxicity of NAC and perform cost-effectiveness analysis. In addition, subset analyses to explore predictors of response to NAC, identify patients more likely to benefit from NAC and assess the potential role of early PET scan will be performed.

**Study design:** Patients with resectable AGC will be eligible for the study. Enrolled patients will be randomized to NAC + surgery (NAC+S) or to surgery alone (S). Randomization sequence will be centrally generated using blocks of variable length and will be available on-line. All data will be entered in e-CRFs developed by the Unit of Clinical Epidemiology of the AOU San Giovanni Battista di Torino, accessible at http://www.epiclin.it. Pre-operative staging procedures, including a baseline FDG-PET, will be performed in both arms. A second PET will be repeated in NAC+S arm only on day 14 from the first cycle of NAC, for early metabolic evaluation. Patients showing a relative reduction of FDG uptake =< 35% as compared to baseline will be considered as non responder. FDG-non avid patients at baseline will be excluded from the second evaluation. This second PET results will be used only for statistical analyses and not for clinical decision.

In NAC+S arm a cycle of Docetaxel 60 mg/m2 iv on day 1, Oxaliplatinum 100 mg/m2 iv on day 1 and Capecitabine 625 mg/m2, given twice daily x os, from day 1 to 21, will be administered every 3 weeks for a total of 3 cycles.

Clinical response at the end of NAC will be assessed according to updated RECIST criteria. Surgery (a controlled D2 gastrectomy) will be performed within 4 weeks from randomization in S arm and within 3 to 6 weeks from the end of the last cycle of NAC in NAC+S arm. Detailed schedules to be filled during procedures will guarantee a standard quality of performed surgery. Histopathological evaluation of the response to NAC will be performed according to Becker’s criteria.

Four to six weeks after surgery, all patients in both arms will receive 3 further cycles of the same chemotherapy regimen. A regular follow up with CT scan twice/year will be performed.

**Material and methods:** A sample size of 360 patients (180 per arm) is needed to demonstrate, with a two-sided logrank test, an improvement of 5-years OS with NAC from 40% to 55%, with 80% power and 5% type I error. We estimate to enroll the patients in 3 years, to ensure a minimum follow-up of 3 years and to perform the final analyses on all randomized patients (intention to treat population), when 172 deaths will be recorded. All time to event endpoints will be compared with the Kaplan Meier method and interactions with patient's characteristics will be explored with a Cox model.

**Main expected results and Impact:** The present study aims to demonstrate a further 15% survival gain also after a complete controlled D2 surgery. Furthermore the early detection of non responder to NAC through biomarkers and PET scan could avoid the administration of unnecessary chemotherapy.