



A phase I-trial assessing several schedules of Oral S-1 combined with fixed doses of Oxaliplatin and Irinotecan in patients with advanced or metastatic digestive adenocarcinoma as first- or second-line treatment

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A phase I-trial assessing several schedules of Oral S-1 combined with fixed doses of Oxaliplatin and Irinotecan in patients with advanced or metastatic digestive adenocarcinoma as first- or second-line treatment

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Introduction: S-1 is a fourth-generation oral fluoropyrimidine based on the combination of Tegafur, converted to 5-fluorouracil (5-FU) in the liver by the cytochrome P450 2A6, with two 5-FU biochemical modulators, namely Gimeracil and Oteracil. Combined S-1 with Irinotecan (Iri) or Oxaliplatin (Ox) was assessed in Asian populations according to biweekly schedules with an acceptable toxicity and efficacy

(Chon et al, 2011, *Cancer Chemother Pharmacol*; Hong et al, 2010, *Cancer Chemother Pharmacol*). SIRINOX is a phase I multicenter trial. Primary objective is to determine the maximum tolerated dose in both SIRI and SIRINOX regimens and the recommended phase II dose of Oral S-1 combined with a fixed dose of Ox and Iri in a biweekly schedule. Secondary objectives are safety, objective response rate, progression-free and overall survival. Ancillary analyses will be conducted on S-1 and Iri pharmacokinetics, as well as on the mutational status of the UGT1A1, DPD and CYP2A6 genes.

Methods: Concerning the SIRI schedule, a standard 3 + 3 design with a dose-escalation of four dose-levels of S-1 is planned (25, 30, 35 and 40mg/m²). S-1 is delivered twice a day from day 1 to day 7, followed by a 7-day recovery period, with a fixed dose of 180mg/m² Iri over 90 minutes IV, on day 1 of each cycle. Three additional patients will be included if a dose limiting toxicity is reported. For the SIRINOX schedule, a standard 3 + 3 design is planned, with 5 dose-levels of S-1 (20 to 40mg/m², with 5mg/m² increments) depending on the SIRI results. Fixed doses of Ox (85mg/m² over 120 minutes IV) and of Iri (180mg/m² over 90 minutes IV) will be delivered at day 1 of every cycle. G-CSF will be given systematically from day 8 to day 13. The first patient was included recently and treated at the first level. The recommended phase II dose will be tested in an expansion cohort of 10 additional patients. Given the therapeutic potential and reduced toxicity advantages of S-1 compared with other fluoropyrimidines, this trial was developed to propose an alternative regimen to FOLFIRI and FOLFIRINOX.

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