Current Trial Report

# Association Between Proton Pump Inhibitors and Metronomic Capecitabine as Salvage Treatment for Patients With Advanced Gastrointestinal Tumors: A Randomized Phase II Trial

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## Abstract

The acidification of extracellular compartment represents a conceivable mechanism of drug resistance in malignant cells. In addition, it has been reported to drive proliferation and promote invasion and metastasis. Experimental evidence has shown that proton pump inhibitors can counteract tumor acidification and restore sensitivity to anticancer drugs. Moreover, early clinical data have supported the role of proton pump inhibitors in anticancer treatments. Metronomic capecitabine has demonstrated beneficial effects as salvage chemotherapy for heavily pretreated or frail patients with gastrointestinal cancer. The present study (EudraCT Number: 2013-001096-20) was aimed at investigating the activity and safety of high-dose rabeprazole in combination with metronomic capecitabine in patients with advanced gastrointestinal cancer refractory to standard treatment. A total of 66 patients will be randomized 1:1 to receive capecitabine 1500 mg/daily, continuously with or without rabeprazole 1.5 mg/kg twice a day, 3 days a week until disease progression, undue toxicity, or withdrawal of informed consent. The primary endpoint is progression-free survival. The secondary endpoints are clinical benefit, which reflects the proportion of patients with complete response, partial response, and stable disease, and overall survival. Progression-free and overall survival will be evaluated using a log-rank test to determine the effect of rabeprazole independently at the 2-sided α-level of 0.05. Other assessments will include the frequency and severity of adverse events and changes in laboratory parameters to measure the safety, and the pharmacokinetics of capecitabine. The results are expected in 2016.

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## Introduction

Extracellular acidity in the cancer microenvironment has a pivotal role in invasion, metastasis, and drug resistance.[1] Indeed, it fosters both the secretion and activation of many proteases involved in the digestion and remodeling of the extracellular matrix. The most important cause of tumor acidity lies in the preeminent, even in the presence of normal oxygen concentrations, anaerobic glucose metabolism (Warburg effect). Lactate production and increased amount of $H^+$ ions prompt pH decrease in the tumor microenvironment and impair the uptake of weakly basic cytotoxic drugs, reducing their therapeutic effectiveness.[1] Thus, increasing the pH of the tumor microenvironment epitomizes an extremely intriguing hypothesis to overcome the multi-drug resistance. Vacuolar $H^+$-ATPases (V-ATPases) are proton exchangers that generate the pH gradient across both the plasma and intracellular organelles membranes by a net consumption of ATP. Tumor cells show enhanced V-ATPases activity compared with their non-transformed counterparts.[2] Moreover, the expression of V-ATPases in chemo-resistant cancer cells is increased and induced by chemotherapeutic agents.[2] It has been demonstrated, in both in vitro and in vivo experiments, that higher proton pump inhibitor (PPI) doses than those used to block $H^+/K^+$-ATPase on gastric parietal cells can also inhibit V-ATPases, modulate tumor acidification, and restore chemotherapeutic sensitivity in drug-resistant cancer cells.[3-5] Moreover, PPIs are proved to be involved with the modulation of autophagy, which, in malignant cells, represents a survival mechanism by recycling nutrients.[6]

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Theoretically, PPIs need to be delivered at intermittent high doses to gain anti-tumor effects. In fact, an acidic microenvironment is necessary for their transformation into active molecules. In vivo experiments have shown that tumor pH shifts toward neutrality after esomeprazole treatment and returns to acidity within 48 hours after treatment discontinuation.[4] Moreover, in an animal model to revert the acidity of the tumor microenvironment, a dose of about 2.5 mg/kg, which is comparable to that used in humans for the Zollinger-Ellison syndrome (160-240 mg/day),[4] has been tested without evidence of systemic toxicity.[1,4]

On account of a metabolism that takes place through non-enzymatic pathways, rabeprazole has both a low potential for drug interactions and a pharmacokinetics that is rather independent from inter-individual variations linked to polymorphisms of CYP2C19 and CYP3A4.[7]

Both in vitro and in vivo experiments have shown that the use of PPIs before chemotherapy increases tumor cell sensitivity of anti-cancer drugs in several histologic types of tumors.[3]

Further preclinical experiences confirmed that treatment with high-dose PPIs sensitizes drug-resistant human tumors to cytotoxic drugs and impairs the vitality of human B-cell tumors, melanoma, and gastric cancer cells.[4,5]

The first proof of concept study about the increase of sensitivity to chemotherapy subsequent to pretreatment with high-dose PPIs in humans has been carried out in patients with osteosarcoma.[8] In this phase II trial, 98 patients received esomeprazole (60 mg/day) for 2 days before neoadjuvant treatment with methotrexate, cisplatin, and adriamycin. The chemosensitizer use of esomeprazole allowed a higher percentage of tumor necrosis with respect to controls. Noteworthy, the highest pathologic response rate was in a cohort of patients with chondroblastic osteosarcoma, where the expected response rate is usually extremely low. The toxicity profile did not differ regardless of PPIs assumption.

A dose-finding phase I trial has investigated the pharmacokinetics of high-dose pantoprazole in combination with doxorubicin in heavily pre-treated patients with advanced solid tumors.[9] Patients received doxorubicin 60 mg/m$^2$ and escalating doses of pantoprazole (80-360 mg) delivered intravenously prior to doxorubicin. A pantoprazole dose of 240 mg was recommended, and it is currently evaluated prior to docetaxel as a first-line treatment in men with castration-resistant prostate cancer (NCT01748500). PPIs have already been tested in metastatic breast cancer.[10] Ninety-four patients were randomized to 3 arms of treatment: arm A, consisting of chemotherapy alone (docetaxel 75 mg/m$^2$ followed by cisplatin 75 mg/m$^2$, every 21 days up to 6 cycles); arms B and C consisting of the same chemotherapy regimen associated with weekly, high-dose esomeprazole (80 mg orally [p.o.] twice a day [b.i.d.] and 100 mg p.o. b.i.d., on days 1-3, respectively). The overall response rate and time to progression were better in patients receiving PPI, especially those with triple-negative breast cancer (TNBC) without additional toxicity. According to such results, a phase II trial (NCT02595372) is testing omeprazole at dosage of 80 mg b.i.d., starting 4-7 days before chemotherapy and continuing until surgery, in the neoadjuvant setting of TNBC.

It has been demonstrated that cytotoxic chemotherapeutic agents can be redirected to an endothelial cell target by changing their dose and frequency of administration.[11] This alternative way of delivering chemotherapy, so called 'metronomic,' has lately exhibited many additional mechanisms of action, such as the stimulation of anti-tumor immunity as well as a direct inhibition of tumor cell growth. Metronomic protocols may also be combined with target agents, maximum tolerated dose chemotherapy (chemo-switch), and even drugs that were not originally developed as anticancer therapy (drug repositioning).[12]

Metronomic capecitabine (mCAP) has been investigated, as a single agent, for the treatment of various advanced tumors after the failure of prior chemotherapy. The best schedule to deliver mCAP, as well as most of the anticancer drugs, has not yet been defined.[13] It has been recently demonstrated that mCAP (1500 mg/day) is a moderately active, well-tolerated regimen as salvage chemotherapy in patients with metastatic gastrointestinal cancer.[14,15]

According to the aforementioned background, we set up a prospective, randomized, phase II clinical trial, aimed at investigating whether PPIs can improve the activity of metronomic chemotherapy in patients with metastatic gastrointestinal cancer, refractory to conventional therapy (EudraCT Number: 2013-001096-20). The overall objective of this study is to evaluate the activity and safety of high-dose rabreprazole combined with mCAP in patients with refractory gastrointestinal cancer after failure of standard treatments.

## Discussion

### *Study Design*

This is a mono-institutional, open label, randomized phase II study in which eligible patients are randomly assigned 1:1 to capecitabine, 1500 mg/daily, continuously with or without rabeprazole 1.5 mg/kg b.i.d., 3 days a week. The eligibility criteria are described in Table 1. In Figure 1 both mechanisms of action and the schedule of the combination regimen have been reported. The primary end-points of the study were the safety and activity of the combination regimen compared with mCAP alone. The local independent ethics committee approved the study design.

### *Study Endpoints*

This study was designed with the primary endpoint of 3-month progression-free survival (PFS). PFS will be defined as the interval from the first dose of the study drug to the date of the first

**Table 1** Inclusion and Exclusion Criteria

| Inclusion Criteria | Exclusion Criteria |
|---|---|
| Pre-treated patients with advanced gastrointestinal tumors | Gastrointestinal tumors that can be treated with standard treatments |
| Performance status (ECOG) ≤2 | Cardiovascular or CNS disease |
| Life expectancy >3 months | Previously untreated CNS metastases |
| Adequate organ (liver, kidney, heart, and bone marrow) function | Pregnant or breast-feeding patients |
| Written informed consent form prior to registration | Organ dysfunctions that usually hinder the use of cytotoxic drugs |
| Accessibility for treatment and follow-up | Substance abuse and any other condition that may interfere with patients' participation in the study and evaluation of study results |

Abbreviations: CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group.