The clinical pharmacokinetics of many tyrosine kinase inhibitors (TKIs) is characterized by pH-dependent solubility, and co-administration with gastric acid suppressants in patients taking these types of medications may decrease drug exposure and efficacy (Clin Pharmacol Ther. 2012;92(2):203-13). A pooled analysis conducted across 40 cell carcinoma (mRCC) patients within phase II and III clinical trials showed that the use of proton pump inhibitors (PPIs) on concomitant TKIs could negatively affect the efficacy and safety of selected antiangiogenic drugs, including sunitinib, axitinib, and sorafenib (Clin Genitourin Cancer. 2017;15(6):724-732). In a pharmacokinetic study carried out in a small cohort of patients with solid tumors treated with pazopanib and esomeprazole, the area under the concentration-time curve (AUC) and maximum concentration (Cmax) of pazopanib were reduced by 40% and 42%, respectively (Cancer Chemother Pharmacol. 2013;71(6):1635-4). Furthermore, it has been demonstrated that the minimum concentration (Cmin) levels of pazopanib were lower in patients who received PPIs, as compared with non-users (Int J Cancer. 2021;146(11):2799-2806). The current study aims to investigate the effect of concomitant PPIs on pazopanib progression free survival (PFS) in patients affected by mRCC.

Patients and Methods
mRCC patients candidate to pazopanib as first line treatment were enrolled in this retrospective observational study. Patients were defined as «no concomitant PPIs» if no PPIs were administered during pazopanib treatment and as «concomitant PPIs» if the administration of PPIs covered the entire or not less than 2/3 of treatment with pazopanib. All clinical interventions were made according to clinical practice.

Results
A total of 126 patients were enrolled; median PFS to pazopanib was 12 months. Fifty-nine patients belonged to «no concomitant PPIs» during pazopanib treatment and 67 to the «concomitant PPIs» group. Most prescribed PPIs were lansoprazole and pantoprazol. The overall population was stratified according to PFS, showing no difference in the two groups (p=0.95). Patients were then stratified based on median PFS as «short» (n=70) and «long» (n=56) responders. In the long responders group, there was a significant difference in terms of PFS in patients assuming vs not assuming Pazopanib PFS=12 months; n=70 and <long> PFS=12 months; n=56 responders. Patients divided in the two groups were again stratified accordingly to PPIs yes/no assumption. Interestingly, in the long responders group, there was a significant difference in terms of PFS in patients assuming vs not assuming PPIs, being 24.7 vs 45.5 months, respectively (n=35 vs 21, p=0.03). All statistical analyses were performed with MedCalc Statistical Software version 14.8.1 (MedCalc Software, bvba, Ostend, Belgium).

Conclusions
This study demonstrates that concomitant use of PPIs in mRCC patients treated with pazopanib for long time has a detrimental effect on PFS. Therefore, it is recommended to prescribe PPIs with strict compliance with the registered indications and for short periods, or use alternative gastroprotective procedures.