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Mir, O., Touati, N., Lia, M. et al. (11 more authors) (2019) Impact of concomitant administration of gastric acid-suppressive agents and pazopanib on outcomes in soft-tissue sarcoma patients treated within the EORTC 62043/62072 trials. *Clinical Cancer Research*, 25 (5). pp. 1479-1485. ISSN 1078-0432

<https://doi.org/10.1158/1078-0432.CCR-18-2748>

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Research article

Impact of concomitant administration of gastric acid suppressive agents and pazopanib on outcomes in soft tissue sarcoma patients treated within the EORTC 62043/62072 trials.

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Word count: 2432 Tables: 3 Figures: 2 Online supplementary data: 1file

Key words: sarcoma; soft tissue neoplasms; pazopanib; proton pump inhibitors; histamine H2 blockers; pharmacology.

Funding source: This publication was supported by Fonds Cancer (FOCA) from Belgium.

Acknowledgements: EORTC Soft Tissue and Bone Sarcoma Group, and EORTC staff.

Conflict of interest statement:

Dr. Mir has acted as consultant for Amgen, Bayer, BMS, Eli-Lilly, Ipsen, Lundbeck, MSD, Novartis, Pfizer, Roche, Servier and Vifor Pharma.

Dr. Mathijssen received research funding from Astellas, Bayer, Boehringer-Ingelheim, Cristal Therapeutics, Novartis, Pfizer, Prostate, Roche, and Sanofi, and received speaker's fee from Astellas.

Prof. Blay received research funding and honoraria from Bayer, GSK, Pfizer and Novartis.

Dr. Van der Graaf received research funding from Novartis.

Dr. Le Cesne has acted as consultant for Amgen, Bayer, Eli-Lilly, Novartis, Pfizer and PharmaMar.

Other authors have no conflict of interest.

ABSTRACT

Purpose : Pazopanib is active in soft tissue sarcoma (STS). Since pazopanib absorption is pH-dependent, co-administration with gastric acid suppressive (GAS) agents such as proton pump inhibitors could affect exposure of pazopanib, and thereby its therapeutic effects.

Experimental design : The EORTC 62043 and 62072 were single-arm phase II and placebo-controlled phase III studies, respectively, of pazopanib in advanced STS. We first compared the outcome of patients treated with pazopanib with or without GAS agents for $\geq 80\%$ of treatment duration, and subsequently using various thresholds. The impact of concomitant GAS therapy was assessed on progression free survival (PFS) and overall survival (OS) using multivariate Cox models, exploring and comparing also the potential effect on placebo-treated patients.

Results : Of 333 eligible patients, 59 (17.7%) received concomitant GAS therapy for $>80\%$ of pazopanib treatment duration. Median PFS was shorter in GAS therapy users versus no-users: 2.8 vs. 4.6 months, respectively (HR=1.49 [95%CI 1.11-1.99], $p=0.01$). Concomitant administration of GAS therapy was also associated with a shorter median OS: 8.0 vs. 12.6 months (HR=1.81 [95%CI 1.31-2.49], $p<0.01$). The longer the overlapping use of GAS agents and pazopanib, the worse the outcome with pazopanib. These effects were not observed in placebo-treated patients (HR=0.82 [95%CI 0.51-1.34, $p=0.43$] for PFS and HR=0.84 [95%CI 0.48-1.48, $p=0.54$] for OS).

Conclusions : Co-administration of long-term GAS therapy with pazopanib was associated with significantly shortened PFS and OS. Withdrawal of GAS agents must be considered whenever

possible. Therapeutic drug monitoring of pazopanib plasma concentrations may be helpful for patients on pazopanib and GAS therapy.

Translational relevance : (137 words)

Pazopanib is approved for the treatment of advanced soft-tissue sarcoma (STS) pre-treated with doxorubicin-based regimens, based on an increase in progression-free survival, but not in overall survival (OS).

From a pharmacological point of view, pazopanib absorption is pH-dependent, and co-administration with gastric acid suppressive (GAS) agents (such as proton pump inhibitors) negatively affects pazopanib plasma concentrations. Herein, we investigated whether GAS agents could affect outcomes of STS patients treated with pazopanib in the EORTC phase II and III trials.

We found that co-administration of long-term GAS therapy with pazopanib was associated with significantly shortened PFS and OS, possibly due to sub-optimal plasma concentrations.

We conclude that withdrawal of GAS agents must be considered whenever possible in STS patients treated with pazopanib. Monitoring of pazopanib plasma concentrations may be helpful for patients on pazopanib and concomitant GAS therapy.

Introduction

Although gastric acid suppressive (GAS) agents such as proton pump inhibitors (PPI) or histamine H₂-receptor blockers (H₂B) are used in 20-50% of patients undergoing cancer treatment [1], the importance of gastric acid-mediated drug-drug interactions might be underestimated by medical oncologists and prescribing physicians.

Because of the oral administration route of various molecular targeted therapies, including multi-tyrosine kinase inhibitors (TKIs), drug–drug interactions concerning gastrointestinal absorption have become apparent [2]. Indeed, many TKIs show pH-dependent solubility in the physiologically relevant pH range, and their solubility might be decreased by the co-administration of GAS agents, which increase gastric pH [3]. Such drug-drug interactions could reduce the systemic exposure of TKIs, resulting in sub-therapeutic exposure levels, and lead to loss of therapeutic benefit. [2, 4].

Pazopanib is an orally administered, potent TKI targeting the vascular endothelial growth factor receptors (VEGFR)-1, -2, and -3, platelet-derived growth factor receptors (PDGFR)- α and $-\beta$, and KIT. It is approved for the treatment of patients with advanced non-adipocytic soft tissue sarcoma (STS) who have received prior chemotherapy for metastatic disease, based on the combined results of the EORTC 62072 (PALETTE) phase III and 62043 phase II trials [5, 6].

The absorption of pazopanib is pH-dependent, and pazopanib is practically insoluble (<0.1 mg/ml) at pH >4 [2]. In a post-marketing drug-drug interactions study investigating the effect of

increased gastric pH on the pharmacokinetics of pazopanib, pazopanib 800mg OD was given as monotherapy for 7 days followed by pazopanib 800mg OD in combination with the PPI esomeprazol 40mg OD for 5 consecutive days. The combined use of pazopanib and esomeprazol resulted in a decrease in the average maximum pazopanib plasma concentration and the average area under the concentration time curve 24 hours post-dose by 42% and 40%, respectively [7].

Retrospective data suggest that low plasma concentrations of pazopanib (through steady-state concentration $< 20.5 \mu\text{g/mL}$) are associated with poor outcomes in renal-cell carcinoma [8]. This was recently confirmed for renal cell cancer in terms of progression free survival (PFS), and a similar trend was observed in STS patients [9]. This means that a threshold for pazopanib activity likely exists for both tumor types.

Based on this literature, we conducted a retrospective review of the EORTC 62043 and 62072 databases, in order to investigate the association between the use of GAS therapy and clinical outcomes in STS patients treated with pazopanib.

Patients and methods

Study design

The present analysis combined the data from the completed trials EORTC phase II 62043 and phase III 62072 [5, 6]. Both studies were conducted in accordance with the declaration of Helsinki, after approval by institutional review boards, and written consent was obtained from all the subjects.

A per protocol approach was adopted using the following patient inclusion criteria: i) patients eligible in their respective trial, ii) patients who did not have liposarcoma, due to their ineligibility for the phase III study based on the phase II results, iii) patients who started their allocated pazopanib treatment.

Objectives and endpoints

The main objective of the current analysis was to assess the potential presence of an association between the use of GAS agents during pazopanib administration and clinical outcomes. Primary and secondary endpoints were PFS and overall survival (OS), and were calculated from the date of registration/randomization to the first documentation of progression/death and the date of death, respectively. Patients alive at the time of clinical cut-off were censored at the date of last follow-up.

GAS therapy embraced both PPI and histamine H2 blocking medications for which the considered drugs are listed in Supplementary Table 1. The percentage of the pazopanib

administration period during which there was an overlapping administration of GAS therapy was used to classify patients between users and non-users of GAS agents. Based on preparatory investigations, a threshold of 80% was selected upfront to differentiate between these patient groups. Exploratory analyses were performed to investigate the impact of this threshold choice on the estimated models.

An additional objective was to examine whether co-administration of GAS therapy had an attenuating effect on pazopanib-specific toxicities such as hypertension, skin toxicities (alopecia, hypopigmentation, skin rash) or thyroid dysfunction. Definitions of these toxicities are detailed in the supplementary data.

Statistical analysis

Hazard ratios (HR) - with their associated 95% confidence intervals (CI) - were estimated from a multivariate Cox regression model adjusting for performance status (0 vs. 1), gender (male vs. female), tumor grade (low vs. intermediate vs. high) and age at randomization (≤ 50 yrs vs. > 50). The related 2-sided Logrank test p-value and Kaplan-Meier curves were displayed. In order to evaluate the real impact on the drug-drug interaction on the obtained results, similar analyses were conducted on placebo-treated patients from the phase III study, to discriminate for a false effect of GAS therapy on pazopanib treatment outcome, in addition of multivariate sensitivity analyses adjusting for GAS therapy administration at baseline as well. Analyses were performed using SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

GAS therapy administration

A total of 333 patients treated with pazopanib - 118 from the 62043 trial and 215 from the 62072 trial - were eligible for this study. Median follow-up from registration/randomization was 27.6 months (IQR: 22.9-35.4). Among them, 117 (35.1%) received GAS therapy at least once during their pazopanib treatment administration period and 59 (17.7%) of them concomitantly for >80% of the pazopanib duration (Table 1). Nineteen (5.7%) patients were already receiving GAS therapy at the time of registration. Patients baseline characteristics are depicted in Supplementary Table 2.

Effect of concomitant use of pazopanib and GAS agents

Two patients were excluded from multivariate analyses due to missing tumor grade status. As shown in Table 2, the concomitant administration of GAS therapy and pazopanib (>80% threshold) had a significant detrimental effect on PFS (HR=1.49, 95% CI 1.11-1.99, p-value 0.008), with a median PFS of 2.8 months in GAS therapy users versus 4.6 months in non-users (Figure 1A). Male gender and higher tumor grade were associated with shorter PFS as well. From Figure 2, the risk of progression/death increased with the duration of GAS therapy taken concomitantly with pazopanib. By adjusting for the use of GAS therapy at baseline, the primary analysis was not significant at an >80% threshold but the observed trend remained (see supplementary Figure 1).

Similarly, a significant negative effect of the concomitant administration of GAS therapy and pazopanib on OS was observed (HR=1.81, 95% CI 1.31-2.49, p-value <0.001), even with a low

threshold value (see Table 2 and Figure 1B and 2). A longer period of overlap of GAS agents' intake along with pazopanib administration has a detrimental effect on OS (Figure 2).

Sensitivity analysis on Placebo-treated patients

A total of 110 patients within the placebo-treated patients of the 62072 study were eligible for the sensitivity analyses. Among them, 33 (30%) received GAS therapy at least once during their pazopanib treatment administration period and 24 (21.8%) of them concomitantly for >80% of the pazopanib duration (Table 1). Median follow-up from registration/randomization for placebo-treated patients was 25.1 months (IQR: 22.7-28.9). Unlike the pazopanib-treated population, no association was observed between concomitant administration of GAS therapy/placebo and PFS (HR=0.82, 95% CI 0.51-1.34, p-value 0.43 for threshold >80%, Table 3, Figure 1C and 2), as well as OS (HR=0.84, 95% CI 0.48-1.48, p-value 0.547 for threshold >80%, Table 3, Figure 1D and 2), ignorant of the threshold used.

Impact on pazopanib-related toxicities

No relevant differences in the frequency of pazopanib-related toxicities were observed between patients who received or did not receive GAS therapy concurrent with their pazopanib treatment (threshold >80%). Summary results of these analyses are presented in Supplementary Tables 3 and 4.

Discussion

The aim of this study was to investigate the potential effect of concomitant use of GAS therapy and pazopanib treatment on the clinical outcome of STS patients. For the primary analysis, we chose upfront to consider that a patient was a concomitant GAS therapy/pazopanib user if more than 80% of the pazopanib treatment administration period overlapped with GAS therapy prescriptions. This threshold included enough patients in each group (user vs non-user) to estimate any possible association. Chu et al 2016 [10] chose a threshold value of 20% to determine PPI-treated patients, while another study by Sun et al 2016 [11] considered the presence of concomitant administration when the patient received at least one PPI prescription together with capecitabine. However, a higher threshold value allowed the composition of a more homogeneous group of GAS users, making the occurrence of the expected drug-drug interaction with pazopanib more likely and therefore its potential impact on patient outcome. Moreover, the exploration of the impact of different threshold values on the outcome for concomitant administration neutralized the limitations of a single 80% value choice.

From multivariate analyses, this co-administration of GAS therapy was found to have a negative impact on PFS and OS, for which the severity depended on the period of overlap of GAS agent intake with pazopanib; a longer duration led to a worse prognosis. Furthermore, these effects were not observed in the 62072 trial placebo cohort when using the same analytic approach, which confirmed that the detected impact on clinical outcomes was most likely caused by the drug-drug interaction between GAS therapy and pazopanib.

We consider that the effects of GAS therapy on the pharmacokinetics of pazopanib could account for this observation. Indeed pazopanib has a pH-dependent absorption and is practically insoluble (<0.1 mg/ml) at pH >4 [2]. As a consequence, the increase in gastric pH caused by GAS therapy could decrease pazopanib solubility and absorption, leading to sub-optimal plasma concentrations [3].

Similar findings were reported in the PAZOGIST trial, a randomized phase 2 study of pazopanib in patients with advanced GIST [12]. In this trial, patients with a past history of gastrectomy had significantly lower plasma concentrations compared to patients without gastrectomy, and shorter PFS.

A possible negative clinical effect of GAS agents on treatment outcomes has also been suggested for other oral anticancer agents with pH-dependent absorption: erlotinib in NSCLC, sunitinib in renal-cell carcinoma, and capecitabine in gastro-esophageal cancer [13, 10, 14]. Moreover, a recent study reported that the concomitant administration of PPIs and capecitabine is associated with an increased risk of recurrence in early stage colorectal cancer patients [11]. All studies conducted on this particular topic recommend avoiding GAS therapy concomitantly with anticancer treatments whenever possible.

Of note, the circadian pattern of gastric pH and the time course during which medications that increase gastric pH have their effect, suggest that timing of pazopanib administration could influence the pazopanib exposure [15]. Therefore, if the concurrent use of a GAS agent is medically necessary during pazopanib treatment, it is currently recommended that the dose of

pazopanib should be taken without food, once daily in the evening, concomitantly with the GAS agent.

As administration of GAS therapy during pazopanib treatment reduced pazopanib efficacy, we undertook an exploratory analysis to assess whether co-administration also had a protective effect against pazopanib-specific toxicities such as hypertension, skin-related toxicities or thyroid dysfunction. In the corresponding analyses shown in the appendix, no consistent differences in occurrence of pazopanib-related toxicities were observed between concomitant GAS-users and non-users. Only slight distinctions were reported around skin toxicities but this analysis was further limited by the low overall incidence of adverse events.

As in previous research on this topic, our study has some limitations [16]. First of all, the retrospective nature of the present study did not permit investigation of the respective timings of administration of GAS therapy and pazopanib. In addition, PPI dose and type of PPI was not considered in this study. As the potential to suppress the acidity of the stomach differs for the different PPI variants, this could be of relevance [17]. Also, it is unknown whether patients have always mentioned their over-the-counter use of GAS therapy given its widespread availability without prescription. Regarding GAS therapy itself, sub-group analyses differentiating PPIs from H2 blocker intake concomitantly to pazopanib were conducted, and a similar impact was observed on patient outcomes for both agents.

As far as pazopanib plasma concentrations are concerned, it has been argued that clinical activity was lower in patients with trough steady-state concentrations $< 20.5 \mu\text{g/mL}$ [8, 9]. In the context of medically necessary GAS therapy, we suggest that therapeutic drug monitoring could help detect patients with sub-optimal plasma exposure. Whether intra-patient pazopanib dose

escalation would improve outcomes in these patients remains unknown, although a recent study has shown the feasibility of such an approach [18]. Furthermore, acidic beverages increase the bioavailability of erlotinib - another TKI with pH-dependent absorption - [19] but the impact in patients taking pazopanib with GAS therapy is currently unknown. Another approach to prevent suboptimal pazopanib exposure could be to use alternative schedules to combine TKI and GAS. This is currently under investigation in at least two clinical trials with TKIs: regorafenib and afatinib (see www.clinicaltrials.gov: NCT02800330 and www.trialregister.nl: NTR6652, respectively, last accessed on Feb 20th, 2018).

One of the main challenges for this study was the approach used to describe this particular type of drug-drug interaction effect. To handle the potential time-dependence relation of the drug, several methods such as landmark analyses, cox models with time-dependent covariates or even landmark supermodels [20] could be used. However, the relatively low number of patients and the complexity of our data made the results not applicable to these models. Moreover, by examining the patient profiles, no apparent link between patterns of GAS therapy administration and the duration of pazopanib treatment was identified, suggesting no specific trend over time. Therefore we preferred to preserve the assumption that the hazard functions are proportional over time and consider the level of co-administration as baseline information, even though this was conceptually inaccurate. Dichotomizing patients between user and non-users was the most intelligible way to illustrate the drug interaction impact. The proportion of concomitant GAS therapy/pazopanib expressed as a continuous covariate has been investigated too, showing a non-significant detrimental effect on PFS (HR=1.04, 95% CI 0.98-1.10, p-value 0.219 for a +20% overlapping augmentation).

In conclusion, in the EORTC 62043 and 62072 trials, 35% of eligible patients took GAS agents at any time during pazopanib treatment, and in half of these patients for over 80% of the duration of their pazopanib treatment. Administration of long duration GAS therapy with pazopanib was associated with both shortened PFS and OS. Therefore, in patients with an indication to start pazopanib, withdrawal of GAS agents must be considered whenever possible, and patients should be warned against taking over the counter GAS medications. If patients have good medical reasons to stay on, or to start, GAS medication, therapeutic drug monitoring of pazopanib plasma concentrations could be helpful to optimally adjust the pazopanib dose.

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Figures legends

Figure 1: Progression-free survival (PFS) and overall survival (OS) in concomitant GAS therapy/administered treatment users (blue curve) versus non-users (red curve) at a threshold of 80%. PFS in pazopanib-treated population (A), OS in pazopanib-treated population (B), PFS in placebo-treated population (C) and OS in placebo-treated population (D).

Pazopanib-treated population: Median PFS = 2.8 months (users) vs. 4.6 months (non-users); Median OS = 8.0 months (users) vs. 12.6 months (non-users). Placebo-treated population: Median PFS = 2.1 months (users) vs. 1.3 months (non-users); Median OS = 10.1 months (users) vs. 10.7 months (non-users)

Figure 2: Evolution of the Hazard Ratio (multivariate analysis) for the effect of concomitant administration of GAS therapy/treatment on progression-free survival (top) and overall survival (bottom) among pazopanib (red) and placebo (blue) patients according to the selected threshold value

Abbreviations: HR, Hazard ratio; CI, Confidence interval. Treatment: Pazopanib or Placebo

Figure 1

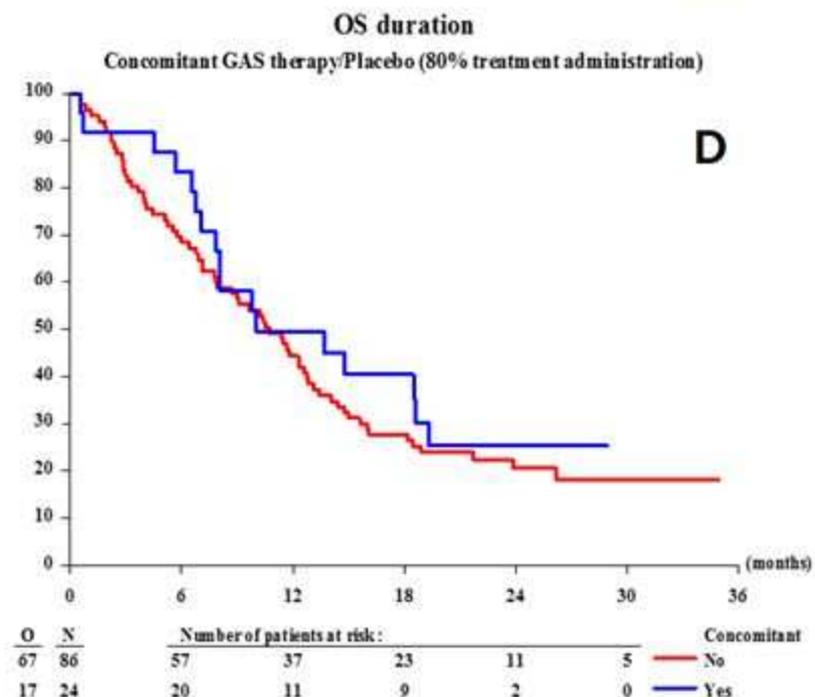
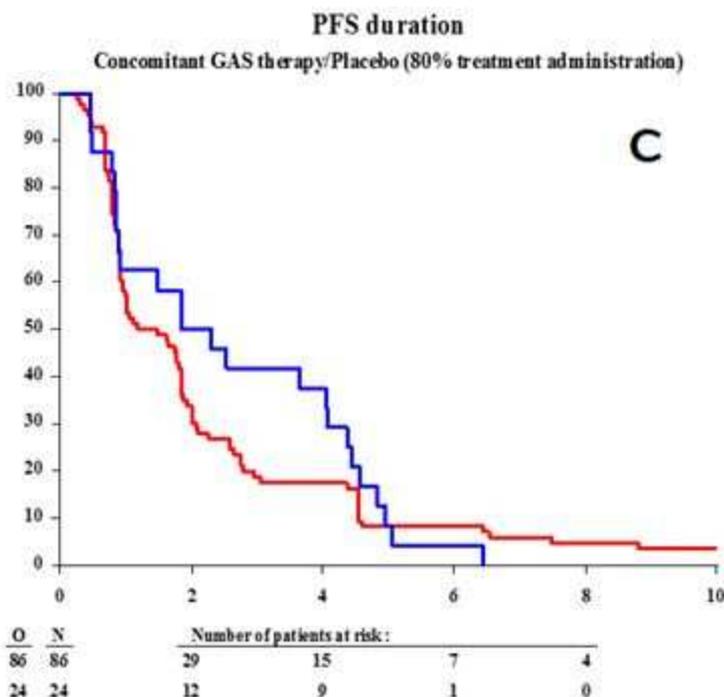
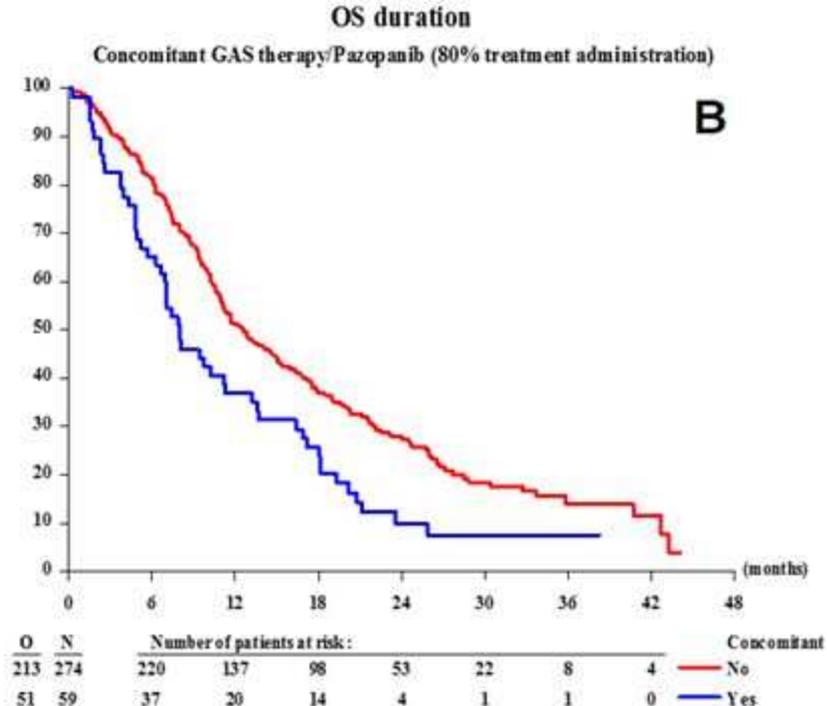
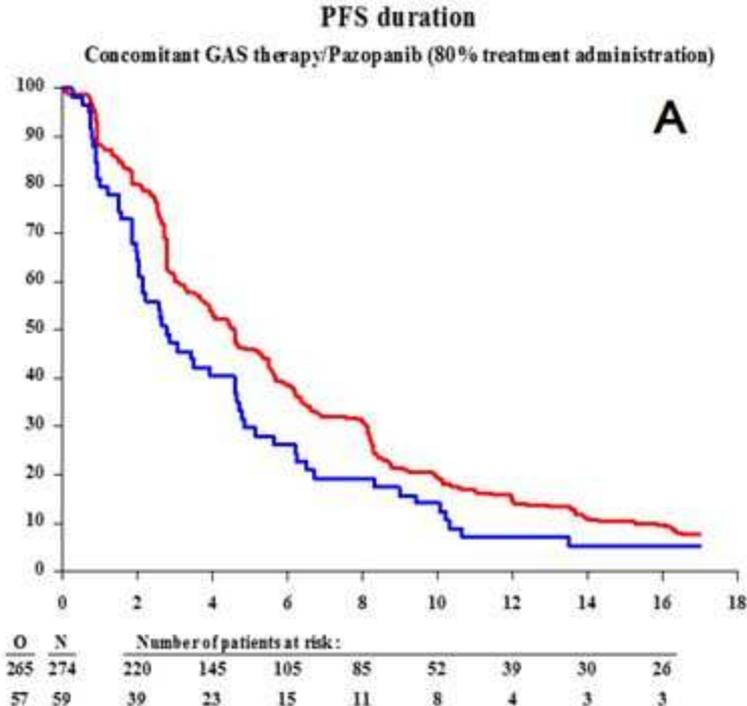


Figure 2

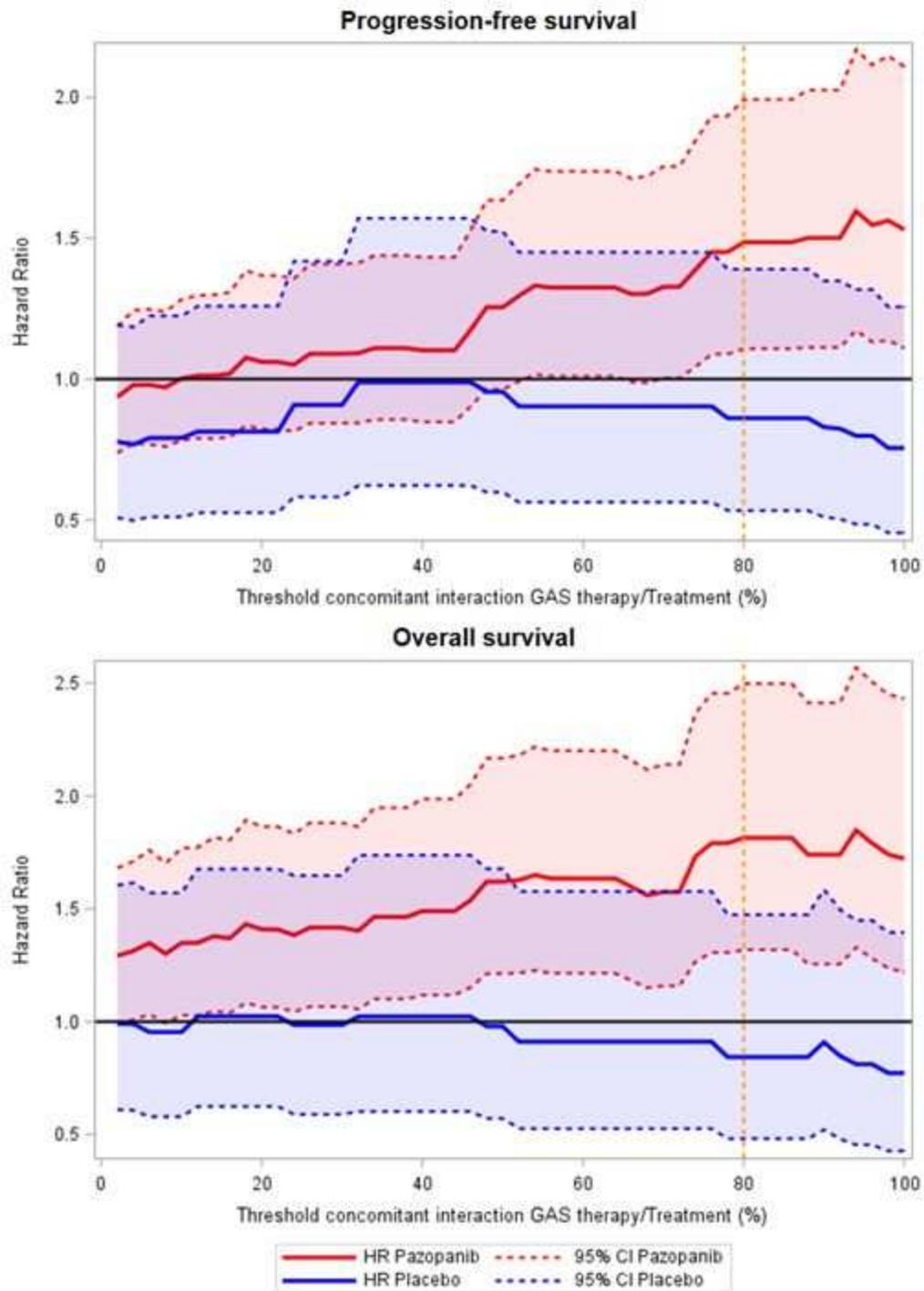


Table 1: Description of GAS therapy received together with protocol treatment in EORTC 62043 and 62072 studies.

	Population on pazopanib			Population on placebo
	62043 (N=118)	62072 (N=215)	Total (N=333)	Total (N=110)
	N (%)	N (%)	N (%)	N (%)
Use of GAS therapy together with treatment				
No GAS therapy	85 (72.0)	131 (60.9)	216 (64.9)	75 (68.2)
GAS therapy	33 (28.0)	84 (39.1)	117 (35.1)	35 (31.8)
PPI	31 (26.3)	63 (28.4)	93 (27.9)	26 (23.6)
H2 blocker	1 (0.8)	19 (8.8)	21 (6.3)	8 (7.3)
PPI & H2 blocker	1 (0.8)	2 (0.9)	3 (0.9)	1 (0.9)
Proportion of treatment duration with concomitant administration of GAS therapy				
No concomitant administration	85 (72.0)	131 (60.9)	216 (64.9)	75 (68.2)
0% < . <= 20%	7 (5.9)	23 (10.7)	30 (9.0)	5 (4.5)
20% < . <= 40%	1 (0.8)	7 (3.3)	8 (2.4)	3 (2.7)
40% < . <= 60%	3 (2.5)	3 (1.4)	6 (1.8)	2 (1.8)
60% < . <= 80%	6 (5.1)	8 (3.7)	14 (4.2)	1 (0.9)
80% < .	16 (13.6)	43 (20.0)	59 (17.7)	24 (21.8)

Abbreviations: GAS, gastric acid suppressive; PPI, proton pump inhibitor; H2B, Histamine H2 blocker.

Table 2: Association between clinical outcomes (PFS/OS) and baseline characteristics/concomitant GAS therapy administration (multivariate cox models) among pazopanib-treated patients.

		Population on pazopanib			Multivariate Cox model for PFS		Multivariate Cox model for OS	
Covariates		Patients* (N=331)	Observed PFS events (O=320)	Observed OS events (O=262)	Hazard Ratio (95% CI)	Wald p-value	Hazard Ratio (95% CI)	Wald p-value
Concomitant administration of GAS therapy/Pazopanib	No	273 (82.5)	264 (82.5)	212 (80.9)	1.00	0.008	1.00	<0.001
	Yes	58 (17.5)	56 (17.5)	50 (19.1)	1.49 (1.11, 1.99)		1.81 (1.31, 2.49)	
Performance status	0	167 (50.5)	161 (50.3)	124 (47.3)	1.00	0.139	1.00	<0.001
	1	164 (49.5)	159 (49.7)	138 (52.7)	1.18 (0.95, 1.48)		1.73 (1.35, 2.22)	
Gender	Male	139 (42.0)	136 (42.5)	117 (44.7)	1.00	0.006	1.00	0.002
	Female	192 (58.0)	184 (57.5)	145 (55.3)	0.73 (0.58, 0.91)		0.68 (0.53, 0.87)	
Tumor grade	Low	28 (8.5)	23 (7.2)	16 (6.1)	1.00	<0.001	1.00	0.001
	Intermediate	109 (32.9)	107 (33.4)	88 (33.6)	1.82 (1.16, 2.88)		2.31 (1.38, 3.89)	
	High	194 (58.6)	190 (59.4)	158 (60.3)	2.33 (1.49, 3.63)		1.66 (0.97, 2.84)	
Age at randomization	≤50 years	133 (40.2)	126 (39.4)	103 (39.3)	1.00	0.414	1.00	0.623
	>50 years	198 (59.8)	194 (60.6)	159 (60.7)	1.10 (0.87, 1.39)		1.07 (0.82, 1.38)	

*: 2 patients are excluded from because of missing tumor grade

Abbreviations: GAS, gastric acid suppressive; PFS, progression-free survival; OS, overall survival. CI, Confidence Interval

Table 3: Association between clinical outcomes (PFS/OS) and baseline characteristics/concomitant GAS therapy administration (multivariate cox models) among placebo-treated patients.

		Population on placebo			Multivariate Cox model for PFS		Multivariate Cox model for OS	
Covariates		Patients (N=110)	Observed PFS events (O=110)	Observed OS events (O=84)	Hazard Ratio (95% CI)	Wald p-value	Hazard Ratio (95% CI)	Wald p-value
Concomitant administration of GAS therapy/Placebo	No	86 (78.2)	86 (78.2)	67 (79.8)	1.00	0.4302	1.00	0.547
	Yes	24 (21.8)	24 (21.8)	17 (20.2)	0.82 (0.51; 1.34)		0.84 (0.48, 1.48)	
Performance status	0	52 (47.3)	52 (47.3)	37 (44.0)	1.00	0.0784	1.00	0.056
	1	58 (52.7)	58 (52.7)	47 (56.0)	1.43 (0.96; 2.12)		1.54 (0.99, 2.40)	
Gender	Male	45 (40.9)	45 (40.9)	35 (41.7)	1.00	0.5801	1.00	0.532
	Female	65 (59.1)	65 (59.1)	49 (58.3)	0.89 (0.58; 1.35)		0.86 (0.55, 1.36)	
Tumor grade	Low	3 (2.7)	3 (2.7)	2 (2.4)	1.00	0.1481	1.00	0.238
	Intermediate	26 (23.6)	26 (23.6)	18 (21.4)	2.93 (0.77; 11.07)		2.27 (0.54, 9.56)	
	High	81 (73.6)	81 (73.6)	64 (76.2)	3.29 (0.96; 11.31)		1.55 (0.34, 7.05)	
Age at randomization	≤50 years	54 (49.1)	54 (49.1)	38 (45.2)	1.00	0.8242	1.00	0.124
	>50 years	56 (50.9)	56 (50.9)	46 (54.8)	0.96 (0.65; 1.41)		1.42 (0.91, 2.24)	

Abbreviations: GAS, gastric acid suppressive; PFS, progression-free survival; OS, overall survival. CI, Confidence Interval