Published OnlineFirst February 14, 2019; DOI: 10.1158/1078-0432.CCR-18-2748

Clinical Cancer Research

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

Olivier Mir[1], Nathan Touati[2], Michela Lia[2], Saskia Litière[2], Axel Le Cesne[1], Stefan Sleijfer[3], Jean-Yves Blay[4], Michael Leahy[5], Robin Young[6], Ron H.J. Mathijssen[3], Nielka P. Van Erp[7], Hans Gelderblom[8], Winette T. Van der Graaf[7,9], and Alessandro Gronchi[10]

Abstract

Purpose: Pazopanib is active in soft-tissue sarcoma (STS). Because pazopanib absorption is pH-dependent, coadministration 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 ≥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 nonusers: 2.8 vs. 4.6 months, respectively [HR, 1.49; 95% confidence interval (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: Coadministration 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.

Introduction

Although gastric acid–suppressive (GAS) agents such as proton pump inhibitors (PPIs) or histamine H2-receptor blockers (H2Bs) are used in 20% to 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 multityrosine 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 coadministration of GAS agents, which increase gastric pH (3). Such drug–drug interactions could reduce the systemic exposure of TKIs, resulting in subtherapeutic 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 -β, and KIT. It is approved for the treatment of patients with advanced nonadipocytic 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 800 mg OD was given as monotherapy for 7 days followed by pazopanib 800 mg OD in combination with the PPI esomeprazol 40 mg OD for 5 consecutive days. The combined use

[1]Gustave Roussy, Sarcoma Group, Villejuif, France. [2]European Organization for Research and Treatment of Cancer, Brussels, Belgium. [3]Erasmus MC Cancer Institute, Rotterdam, the Netherlands. [4]Léon Bérard Cancer Center, Lyon, France. [5]The Christie NHS Foundation Trust, Manchester, United Kingdom. [6]Weston Park Hospital, Sheffield, United Kingdom. [7]Radboud University Medical Centre, Nijmegen, the Netherlands. [8]Leiden University Medical Center, Leiden, the Netherlands. [9]The Institute of Cancer Research and the Royal Marsden NHS Foundation Trust, London, United Kingdom. [10]Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy.

Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

Corresponding Author: Olivier Mir, Gustave Roussy Cancer Campus, Sarcoma Group, 114, rue Edouard Vaillant, 94800 Villejuif, France. Phone: 33142114316; Fax: 33142115238; E-mail: olivier.mir@gustaveroussy.fr

doi: 10.1158/1078-0432.CCR-18-2748

Published OnlineFirst February 14, 2019; DOI: 10.1158/1078-0432.CCR-18-2748

Translational Relevance

Pazopanib is approved for the treatment of advanced soft-tissue sarcoma (STS) pretreated with doxorubicin-based regimens, based on an increase in progression-free survival (PFS), but not in overall survival (OS). From a pharmacologic point of view, pazopanib absorption is pH-dependent, and coadministration 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 patients with STS treated with pazopanib in the EORTC phase II and III trials. We found that coadministration of long-term GAS therapy with pazopanib was associated with significantly shortened PFS and OS, possibly due to suboptimal plasma concentrations. We conclude that withdrawal of GAS agents must be considered whenever possible in patients with STS treated with pazopanib. Monitoring of pazopanib plasma concentrations may be helpful for patients on pazopanib and concomitant GAS therapy.

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 after dose by 42% and 40%, respectively (7).

Retrospective data suggest that low plasma concentrations of pazopanib (through steady-state concentration < 20.5 μg/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 patients with STS 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 cutoff 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 S1. 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 nonusers 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 coadministration 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

HRs—with their associated 95% confidence intervals (CIs)—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 vs. >50 years). The related 2-sided log-rank 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.).

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 (interquartile range, 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 S2.

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 nonusers (Fig. 1A). Male gender and higher tumor grade were associated with shorter PFS as well. From Fig. 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 Fig. S1).

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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 and 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)

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 Figs. 1B and 2). A longer period of overlap of GAS agents' intake along with pazopanib administration has a detrimental effect on OS (Fig. 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 (interquartile range, 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; Figs. 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; Figs. 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 S3 and S4.

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 patients with STS. 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. nonuser) to estimate any possible association. Chu and colleagues (10) chose a threshold value of 20% to determine PPI-treated patients, whereas another study by Sun and colleagues (11) considered the presence of concomitant administration when the patient received at least 1 PPI prescription together with capecitabine. However, a higher threshold value allowed the

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[a] ($N = 331$)	Observed PFS events ($O = 320$)	Observed OS events ($O = 262$)	HR (95% CI)	Wald *P* value	HR (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 y	133 (40.2)	126 (39.4)	103 (39.3)	1.00	0.414	1.00	0.623
>50 y	198 (59.8)	194 (60.6)	159 (60.7)	1.10 (0.87–1.39)		1.07 (0.82–1.38)	

[a]Two patients are excluded because of missing tumor grade.

Published OnlineFirst February 14, 2019; DOI: 10.1158/1078-0432.CCR-18-2748

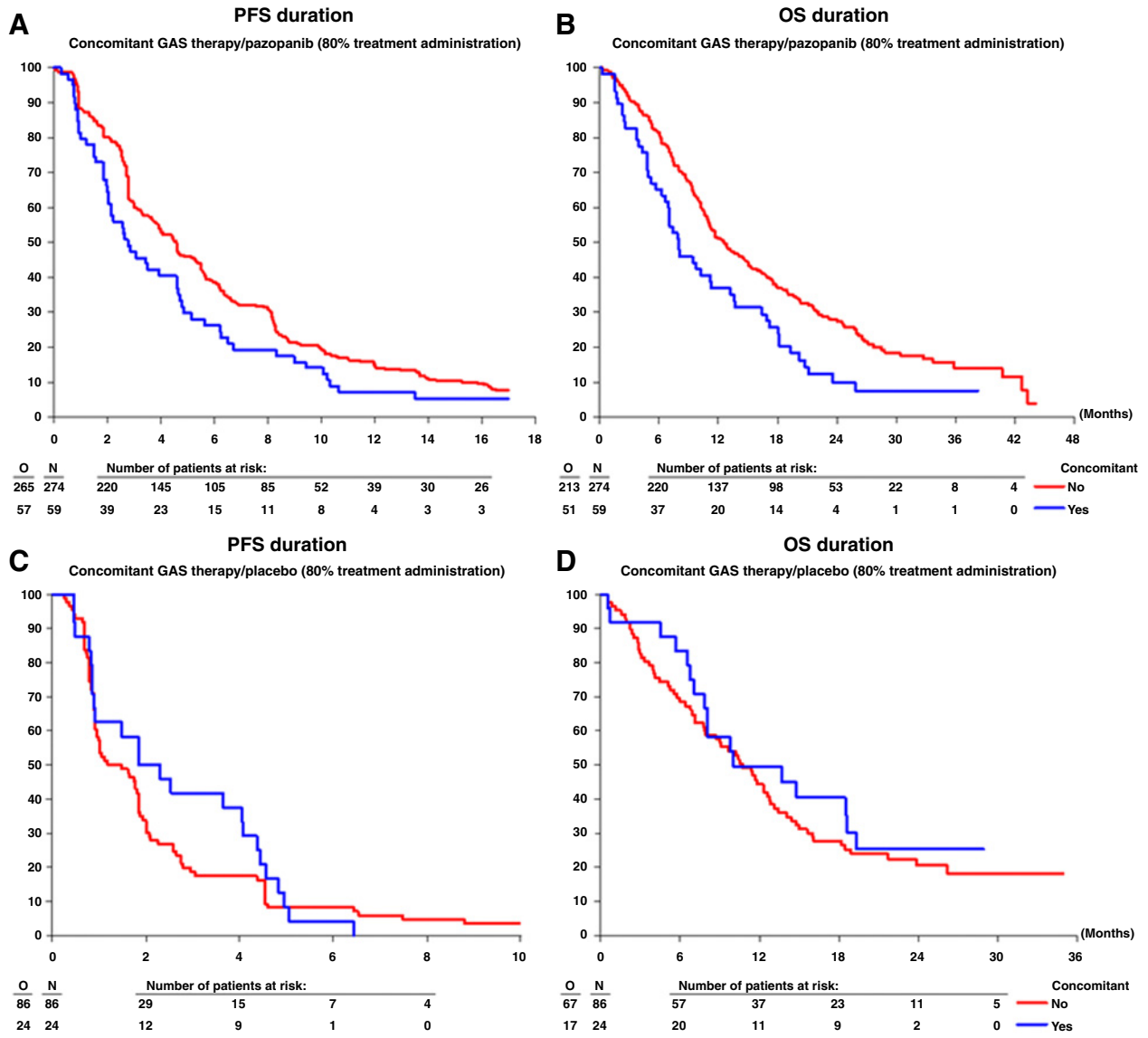

Figure 1.

PFS and OS in concomitant GAS therapy/administered treatment users (blue curve) versus nonusers (red curve) at a threshold of 80%. PFS in the pazopanib-treated population (**A**), OS in the pazopanib-treated population (**B**), PFS in the placebo-treated population (**C**), and OS in the placebo-treated population (**D**). Pazopanib-treated population: median PFS, 2.8 months (users) vs. 4.6 months (nonusers); median OS, 8.0 months (users) vs. 12.6 months (nonusers). Placebo-treated population: median PFS, 2.1 months (users) vs. 1.3 months (nonusers); median OS, 10.1 months (users) vs. 10.7 months (nonusers).

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 coadministration 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 suboptimal plasma concentrations (3).

Similar findings were reported in the PAZOGIST trial, a randomized phase II study of pazopanib in patients with advanced GIST (12). In this trial, patients with a past history of gastrectomy

Published OnlineFirst February 14, 2019; DOI: 10.1158/1078-0432.CCR-18-2748

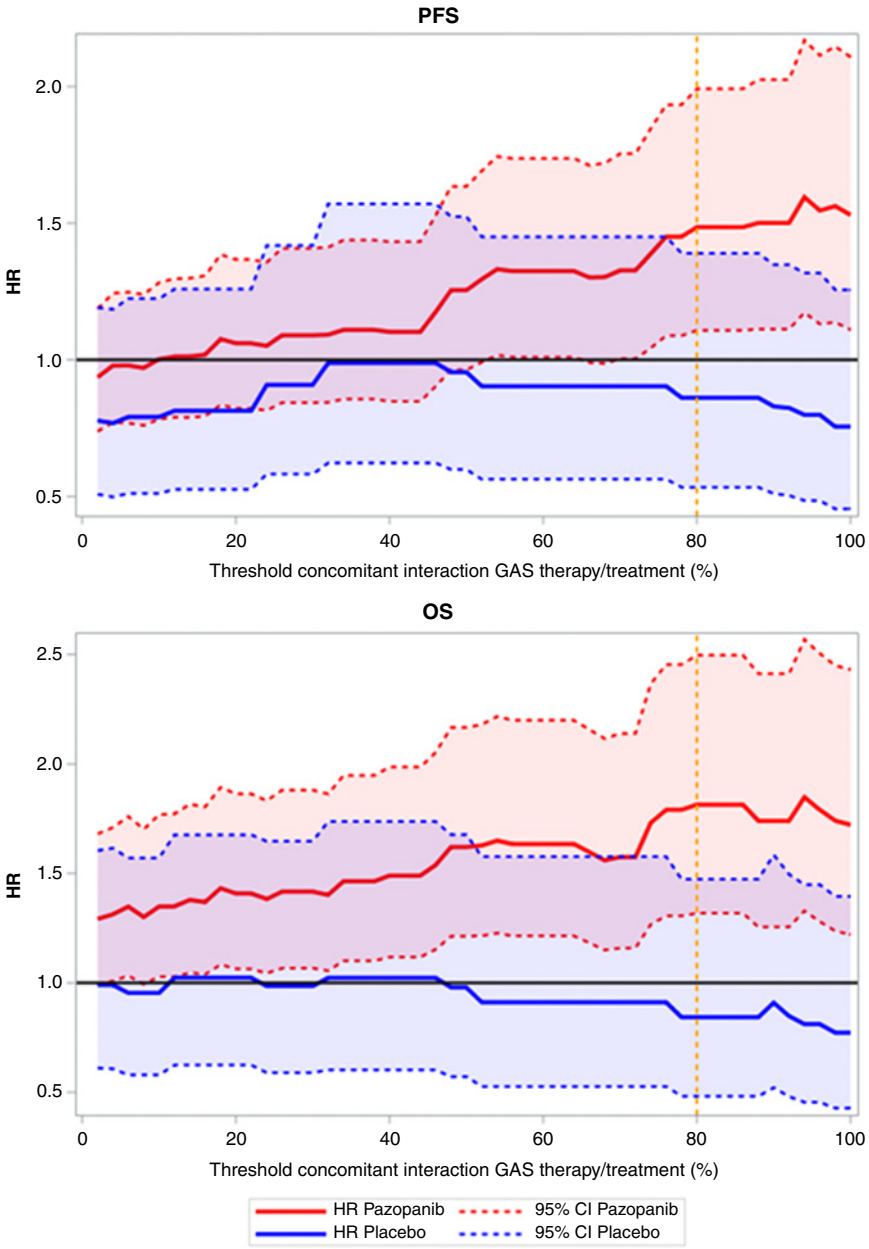

Figure 2.
Evolution of the HR (multivariate analysis) for the effect of concomitant administration of GAS therapy/treatment on PFS (top) and OS (bottom) among pazopanib (red) and placebo (blue) patients according to the selected threshold value.

had significantly lower plasma concentrations compared with 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 non-small lung cancer, 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 coadministration 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 nonusers. Only slight distinctions

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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 ($O = 84$)	HR (95% CI)	Wald *P* value	HR (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 y	54 (49.1)	54 (49.1)	38 (45.2)	1.00	0.8242	1.00	0.124
>50 y	56 (50.9)	56 (50.9)	46 (54.8)	0.96 (0.65–1.41)		1.42 (0.91–2.24)	

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 were 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, subgroup 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 μg/mL (8, 9). In the context of medically necessary GAS therapy, we suggest that therapeutic drug monitoring could help detect patients with suboptimal plasma exposure. Whether intrapatient 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, 21)—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 2 clinical trials with TKIs: regorafenib and afatinib (see www.clinicaltrials.gov: NCT02800330 and www.trialregister.nl: NTR6652, respectively, last accessed on February 20, 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 coadministration as baseline information, even though this was conceptually inaccurate. Dichotomizing patients between user and nonusers 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 nonsignificant 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.

Disclosure of Potential Conflicts of Interest

O. Mir has ownership interests (including patents) at Amplitude Surgical and Transgene, reports receiving speakers bureau honoraria from Eli-Lilly, Roche, Pfizer, and Servier, and is a consultant/advisory board member for Amgen, Bayer, Bristol-Myers Squibb, Eli-Lilly, Ipsen, Lundbeck, MSD, Novartis, Pfizer, Roche, Servier, and Vifor Pharma. A. Le Cesne reports receiving speakers bureau honoraria from Pharmamar, Pfizer, Novartis and Lilly. J.-Y. Blay is a consultant/advisory board member for Novartis and reports receiving commercial research support from GlaxoSmithKline and Novartis. R.H.J. Mathijssen reports receiving speakers bureau honoraria from and reports receiving commercial research support from Novartis. A. Gronchi is a consultant/advisory board member for Novartis, Pfizer, Bayer, Pharmamar, Lilly, and Nanobiotix, and reports receiving commercial research support from Pharmamar. No potential conflicts of interest were disclosed by the other authors.

Published OnlineFirst February 14, 2019; DOI: 10.1158/1078-0432.CCR-18-2748

Authors' Contributions

Conception and design: O. Mir, N. Touati, M. Lia, S. Litière, A. Le Cesne, J.-Y. Blay, R. Young, H. Gelderblom, W.T. Van der Graaf, A. Gronchi
Development of methodology: O. Mir, N. Touati, M. Lia, S. Litière, J.-Y. Blay
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): O. Mir, M. Lia, S. Litière, A. Le Cesne, S. Sleijfer, J.-Y. Blay, M. Leahy, H. Gelderblom, W.T. Van der Graaf
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): O. Mir, N. Touati, S. Litière, A. Le Cesne, S. Sleijfer, J.-Y. Blay, R. Young, R.H.J. Mathijssen, A. Gronchi
Writing, review, and/or revision of the manuscript: O. Mir, N. Touati, S. Litière, A. Le Cesne, S. Sleijfer, J.-Y. Blay, M. Leahy, R. Young, R.H.J. Mathijssen, N.P. Van Erp, H. Gelderblom, W.T. Van der Graaf, A. Gronchi
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): O. Mir, N. Touati, S. Litière
Study supervision: O. Mir, S. Litière, A. Le Cesne, A. Gronchi

Acknowledgments

This study was supported by EORTC Soft Tissue and Bone Sarcoma Group, EORTC staff, and Fonds Cancer (FOCA) from Belgium.

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Received August 22, 2018; revised November 5, 2018; accepted December 14, 2018; published first February 14, 2019.

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Clin Cancer Res Published OnlineFirst February 14, 2019.