The impact of a 1-hour time interval between pazopanib and subsequent intake of gastric acid suppressants on pazopanib exposure

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Abstract
Co-treatment with gastric acid suppressants (GAS) in patients taking anticancer drugs that exhibit pH-dependent absorption may lead to decreased drug exposure and may hamper drug efficacy. In our study, we investigated whether a 1-hour time interval between subsequent intake of pazopanib and GAS could mitigate this negative effect on drug exposure. We performed an observational study in which we collected the first steady-state pazopanib trough concentration ($C_{\text{min}}$) levels from patients treated with pazopanib 800 mg once daily (OD) taken fasted or pazopanib 600 mg OD taken with food. All patients were advised to take GAS 1 hour after pazopanib. Patients were grouped based on the use of GAS and the geometric (GM) $C_{\text{min}}$ levels were compared between groups for each dose regimen. Additionally, the percentage of patients with exposure below the target threshold of 20.5 mg/L and the effect of the type of PPI was explored. The GM $C_{\text{min}}$ levels were lower in GAS users vs non-GAS users for both the 800 and 600 mg cohorts (23.7 mg/L [95% confidence interval [CI]: 21.1-26.7] vs 28.2 mg/L [95% CI: 25.9-30.5], $P = .015$ and 26.0 mg/L [95% CI: 22.4-29.7] vs 30.2 mg/L [95% CI: 28.0-32.5], $P = .007$ for 800 and 600 mg, respectively). This suggests that a 1-hour time interval between pazopanib and GAS may mitigate the negative effect of GAS on pazopanib exposure.

Abbreviations: ATPase, adenosine triphosphatase; $C_{\text{min}}$, trough concentration; CYP, cytochrome P450; GAS, gastric acid suppressants; GM, geometric mean; H2A, histamine-2-receptor antagonists; PFS, progression-free survival; PPI, proton pump inhibitor; RCC, renal cell carcinoma; STS, soft-tissue sarcoma; TDM, therapeutic drug monitoring; TKI, tyrosine kinase inhibitor.

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30.3] vs 33.5 mg/L [95% CI: 30.3-37.1], \( P = .006 \)). Subtherapeutic exposure was more prevalent in GAS users vs non-GAS users (33.3% vs 19.5% and 29.6% vs 14%). Sub-analysis showed lower GM pazopanib \( C_{\text{min}} \) in patients who received omeprazole, while minimal difference was observed in those receiving pantoprazole compared to non-users. Our research showed that a 1-hour time interval between intake of pazopanib and GAS did not mitigate the negative effect of GAS on pazopanib exposure and may hamper pazopanib efficacy.

**KEYWORDS**
drug-drug interaction, gastric acid-suppressive agents, omeprazole, pantoprazole, pazopanib, pharmacokinetics

### 1 INTRODUCTION

Pazopanib is an oral multitargeted tyrosine kinase inhibitor (TKI) registered as monotherapy for the treatment of advanced or metastatic renal cell carcinoma (RCC) and for patients with advanced soft-tissue sarcoma (STS) who received prior chemotherapy.\(^1\)\(^-\)\(^3\) As for most oral targeting TKIs, the exposure of pazopanib is highly variable between patients (40%-70%) and the level of systemic exposure appears to be associated with its clinical effect.\(^4\)\(^-\)\(^10\) For pazopanib, Suttle et al found an association between a pazopanib trough concentration \( C_{\text{min}} \) level of >20.5 mg/L and improved progression-free survival (PFS) in patients with advanced RCC.\(^11\) This exposure-response target has been confirmed in a real-world patient cohort of patients with advanced RCC by Verheijen et al.\(^9\) For patients with STS treated with pazopanib, the exposure-response relationship has not yet been confirmed, although a similar trend has been observed.\(^9\)

The high interpatient variability of pazopanib can partly be explained by its slow and incomplete absorption which results in an oral bioavailability of approximately 21%.\(^12\) Pazopanib is registered in a fixed dose of 800 mg once daily taken fasted. The oral route of administration puts pazopanib at high risk of drug absorption interactions. A favourable effect is that the intake of pazopanib with a high caloric meal increases its exposure up to ~2-fold.\(^13\) In previous work from our research group, we demonstrated that the pazopanib dose can be reduced by 25% when taken with a continental breakfast.\(^14\) Based on these results, our clinicians and patients prefer the prescription of 600 mg pazopanib taken with continental breakfast as starting dose. Conversely, a major disadvantage of pazopanib is that substances that increase intragastric pH are likely to reduce its exposure. Pazopanib requires a low intragastric pH for its absorption, as it is slightly soluble in aqueous solutions at pH 1 and practically insoluble above pH 4.\(^15\)

Use of gastric acid suppressants (GAS) such as proton pump inhibitors (PPIs) or histamine-2-receptor antagonists (H2As) is common in patients with cancer.\(^16\) For pazopanib, the influence of concomitant intake with esomeprazole has been investigated by Tan et al.\(^17\) Administration of esomeprazole 12 hours after fasted intake of pazopanib decreased mean pazopanib \( C_{\text{min}} \) levels by 36%.\(^17\) This decrease in exposure puts patients at risk for subtherapeutic exposure and thus possibly treatment failure.

Previously, Mir et al reported a significantly shortened PFS and overall survival in patients with STS who were treated with GAS compared to patients not treated with GAS.\(^18\) In contrast, in patients with advanced RCC, no statistical significant differences in PFS were observed between GAS- and non-GAS users in two real-world cohorts described by McAlister et al and Van de Sijpe et al.\(^19\),\(^20\) However, these studies did not assess pazopanib \( C_{\text{min}} \) levels which might have explained the apparent discrepancy in the observations. Furthermore, only McAlister et al reported the time of intake of GAS in relation to pazopanib administration.

Several strategies have been proposed to mitigate the interaction of TKIs with GAS. These include switching to short acting anti-acids, use of a once-daily regimen and application of a time interval between drug intakes according to the duration of pH elevation.\(^21\) GAS do not elevate intragastric pH over the full 24-hour range and have a lag time before their onset of effect.\(^22\)\(^-\)\(^24\) Therefore, the administration of the GAS 1 hour after intake of pazopanib allows pazopanib to be...
dissolved at the lowest gastric pH. However, this intake strategy has not yet been evaluated clinically. Therefore, in our study, we investigated the influence of a 1-hour time interval between subsequent intake of pazopanib and GAS on pazopanib exposure taken with and without food.

2 | METHODS

2.1 | Patients

This observational study was performed using clinical data and pazopanib $C_{\text{min}}$ levels obtained from patients treated with pazopanib between March 2013 and March 2020. Patients had plasma pazopanib $C_{\text{min}}$ levels measured as part of routine patient care or as part of the DIET study, in which the effect of food on pazopanib pharmacokinetics was invesigated.\(^{14}\) To rule out potential influence from dose optimization, only the first measured steady-state $C_{\text{min}}$ level at dose of 800 mg taken fasted or 600 mg taken with food were included. Steady-state was defined as pazopanib treatment for more than seven consecutive days. For participants of the DIET study, both first measurements of 800 mg fasted and 600 mg taken with food were included. All patients were advised to take GAS 1 hour after pazopanib intake.

2.2 | Data collection

Baseline characteristics were retrospectively retrieved from the electronical health records or retrieved from the prospectively collected case report forms at the start of pazopanib treatment. Missing data at baseline were replaced by the closest value in time up to 21 days before start of treatment or assessed not available. For pazopanib treatment, start date, dose, time of intake, intake with or without food, concomitant use of PPI, H2A, antacids or interacting medicines were collected at start and at the time of first measured steady-state pazopanib $C_{\text{min}}$ level. For patients who were co-treated with a PPI or H2A, type, dose and frequency of this agent were documented. GAS use was defined as use of a PPI or H2A on the days before the first measured pazopanib $C_{\text{min}}$ level. As antacids only have a short duration of action of 30 to 60 minutes and only minimally affect intragastric pH when taken as recommended (2 hours after or 4 hours before pazopanib), users of antacids were considered not being treated with GAS. For evaluation of the time on treatment, the last day of pazopanib treatment and reason of treatment discontinuation were collected. Patients with gastrointestinal abnormalities and patients who used strong inducers or inhibitors of cytochrome p450 (CYP) 3A4 were excluded.

2.3 | Pazopanib quantification, sample collection and calculation of $C_{\text{min}}$

All blood samples were collected and handled as previously reported.\(^{25}\) Pazopanib concentrations were measured using a validated high-performance liquid chromatography coupled with tandem mass spectrometry detection assay.\(^{26}\) Patients who participated in the DIET study had their first pazopanib $C_{\text{min}}$ level measured at predefined moments.\(^{14}\) For patients who were treated with pazopanib in routine care, no predefined sampling moments were set for measuring pazopanib plasma concentrations, although therapeutic drug monitoring (TDM) is standard of care in our clinic and the first measurement is usually performed 2 to 4 weeks after treatment initiation.\(^{25}\) For each sample, the date and time of last intake of pazopanib and plasma sample collection were recorded. In case the sample was not collected 24 hours after intake, the $C_{\text{min}}$ was calculated by the approach described by Wang et al. This approach assumes a monoeponential decline in plasma concentration and uses the interval between the last dose intake and the blood sample and the mean elimination half-life of pazopanib of 31 hours to calculate the $C_{\text{min}}$ level.\(^{27}\)

2.4 | Statistical analysis

Analyses were performed for pazopanib $C_{\text{min}}$ levels both at 800 mg taken fasted and 600 mg taken with food. Patients were divided into two groups: patients who were treated with GAS or patients who were not treated with GAS. Patient characteristics and pazopanib plasma $C_{\text{min}}$ levels were described using descriptive statistics. For the primary outcome, geometric mean (GM) pazopanib $C_{\text{min}}$ levels were calculated per group and compared to an independent samples $t$ test.

To identify potential differences in effect between the different types of GAS, an explorative sub-analysis was performed. In this analysis, the GM pazopanib $C_{\text{min}}$ levels of the two main subgroups of GAS were compared to the group of patients who were not treated with GAS, regarded as the reference group, using Dunnett’s two-sided test to adjust for multiple comparisons. To explore the influence of use of GAS on treatment outcome, the median PFS between the two groups were analysed per tumour type by Kaplan-Meier method and compared statistically using the log rank test. Hazard ratios were estimated using univariate Cox-regression analyses. PFS was defined as the time on treatment until progression or death.

All statistical analyses were performed using IBM SPSS statistics for Windows version 25.0 (IBM Corp, Armonk, NY). Outcomes with $P$ values <.05 were considered to be statistically significant.

3 | RESULTS

3.1 | Pazopanib 800 mg taken fasted

3.1.1 | Patients

From March 2013 to March 2020, for 136 patients, using pazopanib 800 mg taken fasted, a steady-state pazopanib $C_{\text{min}}$ level was
The majority of patients (n = 96) were treated for RCC, 39 patients were treated for soft tissue sarcoma and one for clear cell ovary carcinoma. Out of these 136 patients, 82 (60.3%) patients did not use concomitant GAS, 50 (36.8%) patients used a PPI and 4 (2.9%) patients used an H2A. Of the PPI users, 26 patients used omeprazole, 3 esomeprazole, 19 pantoprazole, 1 rabeprazole and for 1 patient the type of PPI was unknown. Baseline characteristics were comparable between groups and are shown in Table 1.

### 3.1.2 Pazopanib exposure with and without GAS

In patients treated with GAS, pazopanib GM $C_{\text{min}}$ was significantly lower compared to patients who were not treated with GAS ($23.7 \text{ mg/L [95\% CI: 21.1-26.7]}$ vs $28.2 \text{ mg/L [95\% CI: 25.9-30.5]}, P = .015$; Figure 1). This difference remained significant after excluding the four patients who used an H2A. In patients treated with GAS, 33.3% had a $C_{\text{min}}$ below the target threshold of 20.5 mg/L compared to 19.5% of the patients without GAS ($P = .07$).

### 3.1.3 Effect of the type of PPI

In an exploratory subgroup analysis, a lower GM pazopanib exposure was observed in patients treated with omeprazole (n = 26) (GM $C_{\text{min}}$ 22.8 mg/L [95\% CI: 18.8-27.6], $P = .038$), while minimal reduction in pazopanib exposure was observed in those treated with pantoprazole (n = 19) (GM $C_{\text{min}}$ 26.6 mg/L [95\% CI: 22.0-32.2], $P = .8$) compared to patients who were not treated with GAS (Figure 2).

### 3.1.4 Effect of GAS use on treatment outcome

For the exploratory analysis on PFS, follow-up data were available for 94 of 96 patients with advanced RCC, of which 44 (46.8%) were treated with GAS concomitantly. A total of 51 patients stopped pazopanib treatment due to disease progression or death; 24 patients of them used GAS concomitantly. An overview of reasons for

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**TABLE 1** Demographic and clinical characteristics of patients at baseline

| Baseline characteristic         | 800 mg taken fasted (n = 136) | 600 mg taken with food (n = 83) |
|---------------------------------|-------------------------------|---------------------------------|
|                                 | Without GAS (n = 82) n (%)    | With GAS (n = 54) n (%)         | Without GAS (n = 57) n (%)    | With GAS (n = 26) n (%) |
| Median age (range) (year)       | 59 (28-78)                    | 61.5 (45-85)                    | 61 (28-77)                    | 60 (45-85)             |
| Sex Male                        | 50 (61.0)                     | 40 (74.1)                       | 37 (64.9)                     | 18 (69.2)              |
| Median BMI (range) (kg/m²)      | 25.4 (17.2-52.4)              | 25.9 (20.7-40.4)                | 25.7 (18.7-52.4)              | 24.3 (20.7-34.6)       |
| Karnofsky performance score     |                               |                                 |                               |                         |
| 90-100                          | 36 (43.9)                     | 13 (24.1)                       | 22 (38.6)                     | 7 (26.9)               |
| 80-89                           | 35 (42.7)                     | 29 (53.7)                       | 29 (50.9)                     | 15 (61.5)              |
| <80                             | 5 (6.1)                       | 9 (16.6)                        | 2 (3.5)                       | 3 (11.5)               |
| Tumour type                     |                               |                                 |                               |                         |
| RCC                             | 51 (62.2)                     | 45 (83.3)                       | 38 (66.7)                     | 23 (63.9)              |
| STS                             | 30 (36.6)                     | 9 (16.6)                        | 19 (33.3)                     | 3 (11.5)               |
| Other                           | 1 (1.2)                       | 0                               | 0                             | 0                      |
| Histological subtype (RCC)      |                               |                                 |                               |                         |
| Clear cell                      | 28 (54.9)                     | 24 (53.3)                       | 16 (42.1)                     | 7 (26.9)               |
| Non clear cell                  | 23 (45.1)                     | 21 (46.7)                       | 22 (57.9)                     | 16 (69.5)              |
| Previous systemic treatment     | Yes 42 (51.2)                 | 28 (51.9)                       | 30 (52.6)                     | 11 (42.3)              |

Abbreviations: BMI, body mass index; GAS, gastric acid suppressants; RCC, renal cell carcinoma; STS, soft-tissue sarcoma.
treatment discontinuation is listed in Table S1. No significant difference in PFS was observed for patients who were treated with and without GAS (11 vs 12 months, HR 1.13, 95% CI: 0.64-1.78, \( P = .7 \); Figure S1).

Of the 38 patients with STS, follow-up data were available for 34 patients of which 8 (23.5%) were treated with GAS. A total of 25 patients stopped pazopanib treatment due to disease progression or death, of which 7 patients used GAS. The reasons for treatment discontinuation are listed in Table S1. Median PFS was shortened for patients who were treated with GAS compared to those without (17 vs 32 weeks, HR 3.89, 95% CI: 1.44-10.55, \( P = .008 \); Figure S2).

3.2 | Pazopanib 600 mg taken with food

3.2.1 | Patients

For 83 patients, using 600 mg pazopanib taken with food, a steady-state pazopanib \( C_{min} \) level was available, of whom 61 had RCC and 22 had STS. Out of these 83 patients, 26 (31.3%) patients did use GAS concomitantly, 25 patients used a PPI and 1 patient used an H2A. Of the PPI users, 13 patients used omeprazole, 11 pantoprazole and 1 rabeprazole. Additional baseline characteristics are shown in Table 1.

3.2.2 | Pazopanib exposure

In the patients treated with GAS the GM of the pazopanib \( C_{min} \) was 26.0 mg/L (95% CI: 22.4-30.3) compared to 33.5 mg/L (95% CI: 30.3-37.1) \( (P = .006) \) in patients who were not treated with GAS concomitantly (Figure 3).

4 | DISCUSSION

Our study shows that despite using a 1-hour time interval between dosing, co-treatment with GAS still resulted in reduced pazopanib exposure. Although the average pazopanib \( C_{min} \) level was above the target threshold of 20.5 mg/L, a larger proportion of patients co-treated with GAS showed sub-therapeutic pazopanib \( C_{min} \) levels (33.3% vs 19.5%), suggesting that...
GAS on pazopanib compared to patients treated with 800 mg pazopanib taken fasted with GAS and those without GAS was even more pronounced concerning intake, and could negatively affect patient outcome. The interaction studies state that positive findings from retrospective evaluations can provide valuable insights for clinical practice as we demonstrated in our study. Another potential limitation of our study is that there was no formal check if the intake advice was communicated by the oncologist or pharmacist and adhered to by the patient. Although CYP1A2 has a minor role in pazopanib metabolism, induction of CYP1A2 may have contributed to the lower pazopanib exposure. In summary, multiple pharmacological differences may have contributed to the observed differences in effect on pazopanib exposure, but the exact underlying mechanism remains unclear.

Previously, Mir et al described a significant shortened PFS in patients with STS treated with pazopanib and GAS. In our study, pazopanib Cmin levels in patients treated with GAS were significantly lower, which could explain the observed difference in outcome. Likewise, we also observed a shortened PFS in the small group of patients with STS in our analysis. However, it is important to note that STS is a highly heterogeneous disease and the observed difference may also have been caused by differences in response between differences in disease subtypes.

In contrast, we did not observe a difference in PFS for patients with RCC who were treated with and without GAS. This finding is in line with previous reports by McAlister and Van de Sijpe, who showed no significant difference in PFS between patients treated with and without GAS. The percentage of non-GAS patients with subtherapeutic Cmin levels was comparable to previously reported percentages of pazopanib underexposure (16.4%-19.6%). However, in the participating hospitals in our study pazopanib dose optimization could be attributed by this strategy.

The present study has a number of limitations, inherent to its real-world and retrospective setting. First, no a priori sample size calculation was performed as the study was not initially designed for this analysis. A cross-over design would have been a more ideal design given the high interpatient variability of pazopanib. Nevertheless, the sample size and design is comparable to two previous studies performed on this topic. Also, the FDA guideline on clinical drug interaction studies states that positive findings from retrospective evaluations can provide valuable insights for clinical practice as we demonstrated in our study. Another potential limitation of our study is that there may have been differences between the registered and the actual time of pazopanib intake and sample collection. However, since TDM monitoring is well embedded in our clinic, these differences are likely to be small and of limited influence. An important limitation is that there was no formal check if the intake advice was communicated by the oncologist or pharmacist and adhered to by the patient.

In patients treated with 600 mg pazopanib taken with food, the difference in pazopanib exposure between patients who were treated with GAS and those without GAS was even more pronounced compared to patients treated with 800 mg pazopanib taken fasted (GM Cmin 26.0 vs 33.5 mg/L compared to 23.7 vs 28.2 mg/L). This is an unexpected finding, as we assumed that food intake would somewhat diminish the negative effect of GAS on pazopanib absorption due to enhanced solubility in a lipophilic environment. However, the bottleneck of pazopanib absorption is thought to lie within its poor dissolution at higher pH values. In patients without GAS, meal-stimulated gastric acid release after intake of pazopanib with food may provide suitable intragastric pH for pazopanib dissolution. However, in patients who are co-treated with GAS, inhibition of the meal-stimulated gastric acid release by GAS may have hampered pazopanib absorption.

Interestingly, in the explorative sub-analysis, this negative effect of GAS on pazopanib Cmin seemed to be the strongest for patients who used omeprazole, whereas the effect of pantoprazole was limited compared to patients who were not treated with GAS. This difference may be explained by the different pharmacological characteristics of these drugs.

Pantoprazole has a slower inhibition rate of the gastric H+/K+ adenosine triphosphatase (ATPase) compared to omeprazole. In porcine gastric vessels, it took omeprazole 30 minutes to fully inhibit the H+, K+ ATPase, whereas for pantoprazole only 50% inhibition was reached at 45 minutes. The faster rate of inhibition by omeprazole may be a plausible explanation for the observed effect on pazopanib Cmin as pazopanib may have had less time to dissolve at low pH.

Another difference between pantoprazole and omeprazole is their duration of action. However, as omeprazole 20 mg only showed a marginally longer duration of pH elevation >4 compared to pantoprazole 40 mg (49.16% vs 41.94% of the day), this difference is less likely to explain the observed differences on pazopanib Cmin levels.

Omeprazole and pantoprazole are both metabolised by CYP2C19 and to a lesser extent by CYP3A. However, omeprazole is also an inhibitor of CYP2C19 and thus inhibits its own metabolism leading to non-linear pharmacokinetics. The accumulation of omeprazole may have resulted in a longer duration of acid inhibition. Furthermore, omeprazole is a dose-dependent inducer of CYP1A2, whereas pantoprazole does not affect CYP1A2. Although CYP1A2 has a minor role in pazopanib metabolism, induction of CYP1A2 may have contributed to the lower pazopanib exposure. In summary, multiple pharmacological differences may have contributed to the observed differences in effect on pazopanib exposure, but the exact underlying mechanism remains unclear.

FIGURE 4 Geometric mean (95% CI) scatter plots of the individual pazopanib trough concentration (Cmin) levels for patients who were treated with pazopanib 600 mg taken fed without gastric acid suppressants (GAS), with omeprazole and with pantoprazole respectively.
patient. Therefore, there might have been slight differences in the time of intake of the GAS. In addition, PPIs are also available without prescription in drugstores. Although registration of over-the-counter drug use is standard in care in the Netherlands while screening for drug interactions, the use of undocumented GAS cannot be completely excluded. This potential under-reporting of GAS use, however, would have only diluted the observed differences in exposure. Furthermore, we were not able to assess the influence of the dose of the PPIs, for as some patients these details were missing. Last of all, genetic variations in CYP2C19 are known to contribute to variability in gastric acid inhibition by PPIs, particularly at low doses. However, genotyping was not performed in our study. Approximately 5% of the Dutch population has the CYP2C19*17/*17 genotype and these patients may need up to a 5-fold higher PPI dose to achieve sufficient gastric acid suppression. Therefore, including CYP2C19 genotype in future studies may be warranted.

To the best of knowledge, this is the first study that quantified the influence of GAS on pazopanib exposure in a real-world setting. The clinical consequence of reduced exposure could not be fully assessed, as dose-optimization is standard of care in our clinic. However, the negative effect of GAS on pazopanib exposure despite application of a 1-hour time interval between intake remains clinically relevant, especially for clinicians without access to TDM services. When possible, the use of GAS should be avoided in patients taking pazopanib. In patients who still require co-treatment with GAS, application of a 1-hour time interval between pazopanib and GAS in combination with TDM appears a feasible strategy to optimise pazopanib exposure. Alternatively, if possible switching to another TKI with comparable effectiveness which is less dependent of a low intragastric pH for their absorption, for example, sunitinib for RCC.40 may also be an option.

The observed difference between omeprazole and pantoprazole is an interesting finding that warrants prospective validation and elucidation of the underlying mechanism. Currently, we are investigating whether switching omeprazole for pantoprazole in patients with subtherapeutic exposure helps to achieve adequate pazopanib exposure.

Furthermore, the negative interaction with GAS may also be of major importance for other TKIs that require low intragastric pH for optimal absorption, such as gefitinib, erlotinib and dasatinib.23

5 | CONCLUSION

In our study, we found that application of a 1-hour time interval between pazopanib and GAS intake still results in a significantly lower pazopanib exposure. Medical oncologists treating patients should try to avoid the combination of GAS and pazopanib. If use of GAS is unavoidable, the use of pantoprazole might be preferred over omeprazole, with a 1-hour interval between intake as the best known option so far.

CONFLICT OF INTEREST

All mentioned relationships are outside the submitted work. Frank G. A. Jansman has been on an advisory board for Amgen and Servier. Paul Hamberg has been on an advisory board for Bristol-Meyers Squibb, Ipsen, Novartis, Esai, Sanofi, Jansen and Pfizer. Winette T. A. van der Graaf received a research grant from Novartis, has been on an advisory board for Bayer, and has been a consultant for Springworks. Ingrid M. E. Desar received a research grant from Novartis. Nieltje P. van Erp has received research grants from Novartis, Astellas, Janssen-Cilag, Pfizer, Ipsen, has been on an advisory board for Pfizer, and received honoraria from Bayer and Sanofi. Carla M. L. van Herpen has received research grants form AstraZeneca, Bristol-Meyers Squibb, Merck Sharp and Dohme, Merck, Ipsen, Sanofi, and Novartis, has been on an advisory board for Bayer, Bristol-Meyers Squibb, Ipsen, Merck Sharp and Dohme and Regeneron. The other authors declared no potential conflicts of interest (Stefanie D. Krens, Floor J. E. Lubberman, Marthe van Egmond, David M. Burger, Walter L. Vervenne, Hans Gelderblom).

DATA AVAILABILITY STATEMENT

The datasets generated and analysed for the current study are available from the corresponding author on reasonable request.

ETHICS STATEMENT

Our study was performed in accordance with the Declaration of Helsinki (October 2013) and was approved by the Institutional Review Board from the Radboudumc (December 2018; 2018-4617). With consent of our Institutional Review Board and according to Dutch law on medical research (WMO, article 1) no-ethical approval is required when using anonymous data from routine diagnostic databases, as was done for part of the data analysed in our study. The DIET study was registered at ClinicalTrials.gov (NCT02138526).

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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