

**(RESUBMISSION) Pazopanib Exposure Relationship with Clinical Efficacy and Safety in the Adjuvant Treatment of Advanced Renal Cell Carcinoma**

Cora N. Sternberg<sup>1</sup>, Frede Donskov<sup>2</sup>, Naomi B. Haas<sup>3</sup>, Christian Doehn<sup>4</sup>, Paul Russo<sup>5</sup>, Mohamed Elmeliegy<sup>6</sup>, Guillaume Baneyx<sup>7</sup>, Hiya Banerjee<sup>6</sup>, Paola Aimone<sup>7</sup>, and Robert J. Motzer<sup>5</sup>

<sup>1</sup>Department of Medical Oncology, San Camillo Forlanini Hospital, Rome, Italy. <sup>2</sup>Department of Oncology, Aarhus University Hospital, Aarhus, Denmark. <sup>3</sup>Abramson Cancer Center of the Hospital of the University of Pennsylvania, Philadelphia, PA. <sup>4</sup>Urologikum Luebeck, Luebeck, Germany. <sup>5</sup>Memorial Sloan-Kettering Cancer Center, New York, NY. <sup>6</sup>Novartis Pharmaceuticals, East Hanover, NJ; <sup>7</sup>Novartis Pharmaceuticals, Basel, Switzerland.

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**Corresponding Author:** Prof. Cora N. Sternberg, Department of Medical Oncology, San Camillo Forlanini Hospital, Circonvallazione Gianicolense, 87, 00152 Rome, Italy; Phone: +39 06 6641 8008; Fax: +39 06 663 0771; Email: cnsternberg@corasternberg.com; Academic degree(s): MD, FACP

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Currently no adjuvant treatments are approved for locally advanced renal cell carcinoma (RCC) to reduce the risk of disease recurrence following surgical resection of the primary tumor. In the PROTECT study, adjuvant pazopanib at 600 mg daily following nephrectomy did not meet the primary endpoint of improved disease-free survival (DFS) compared with placebo. The current analyses of pazopanib exposure ( $C_{\text{trough}}$ ) showed that higher pazopanib exposure was associated with improved DFS, without an increase in grade 3/4 adverse events with the exception of hypertension. Pharmacokinetic simulations showed overlapping pazopanib exposure with 600 mg and 800 mg doses. The results suggest that patients achieving higher pazopanib  $C_{\text{trough}}$  derived more clinical benefit from adjuvant pazopanib therapy.

**Abstract:** 246 words (limit 250 words)

**Purpose:** PROTECT, a phase III randomized placebo-controlled study, evaluated pazopanib efficacy and safety in the adjuvant RCC setting. The relationship between pazopanib exposure ( $C_{\text{trough}}$ ) and efficacy and safety was evaluated.

**Experimental design:** Evaluable steady-state blood trough concentrations were collected from 311 patients at week 3 or 5 (early  $C_{\text{trough}}$ ), and 250 patients at week 16 or 20 (late  $C_{\text{trough}}$ ). Pazopanib pharmacokinetic (PK) data was analyzed via a population model approach. Relationship between  $C_{\text{trough}}$  or dose intensity and disease-free survival (DFS) was explored via Kaplan-Meier and multivariate analysis. Adverse events (AEs) and AE-related treatment discontinuation proportions were summarized by  $C_{\text{trough}}$  quartiles.

**Results:** Most (>90%) patients with early or late  $C_{\text{trough}}$  data started on 600 mg. Mean early and late  $C_{\text{trough}}$  overlapped across dose levels. Patients with higher early  $C_{\text{trough}}$  quartiles achieved longer DFS (adjusted hazard ratio [HR], 0.58; 95% CI, 0.42–0.82;  $P = 0.002$ ). Patients achieving early or late  $C_{\text{trough}} > 20.5$   $\mu\text{g/mL}$  had significantly longer DFS, not estimable (NE) vs 29.5 months,  $P = 0.006$ , and NE vs 29.9 months,  $P = 0.008$ , respectively. Dose intensity up to week 8 did not correlate with DFS, consistent with population PK model-based simulations showing overlapping pazopanib exposure with 600 mg and 800 mg doses. The proportion of AE-related treatment discontinuation and grade 3/4 AEs, with the exception of hypertension, was not correlated to  $C_{\text{trough}}$ .

**Conclusions:** In the adjuvant setting, higher pazopanib  $C_{\text{trough}}$  was associated with improved DFS, and did not increase treatment discontinuations or grade 3/4 AEs with the exception of hypertension.

## Introduction

Currently no adjuvant treatments are approved for locally advanced renal cell carcinoma (RCC) to reduce the risk of disease recurrence following surgical resection of the primary tumor. Up to 40% of these patients experience recurrence (1). Agents targeting the vascular endothelial growth factor receptor (VEGFR) are effective for patients with advanced RCC, and have recently been investigated in phase III trials in the adjuvant setting (2-4).

Pazopanib is a VEGFR tyrosine kinase inhibitor (TKI) approved for the treatment of advanced RCC at the daily dose of 800 mg (5, 6). The randomized, placebo-controlled phase III PROTECT study (NCT01235962) evaluated pazopanib as an adjuvant treatment for locally advanced RCC following nephrectomy (4). The starting dose was changed from 800 mg daily to 600 mg daily due to a higher-than-expected study treatment discontinuation rate based on a blinded safety monitoring and the assumption that all these discontinuations occurred in the pazopanib arm. This suggested a minimum of 20% discontinuation rate in the pazopanib arm at the time of the safety review (4). At the time the decision to reduce the starting dose was made (based on a blinded safety aggregate), the discontinuation rate was considered high as compared to that observed with pazopanib in the advanced/metastatic setting. The results of the primary endpoint of disease-free survival (DFS) in ITT600 showed no benefit over placebo in the adjuvant setting. Patients in ITT800 had a 31% reduced risk of recurrence or death (secondary endpoint of the study).

In advanced or metastatic RCC, the relationship between exposure and efficacy endpoints have been established for several other approved VEGFR-TKIs. Model-predicted sunitinib steady-

state AUC correlated with longer time to tumor progression and overall survival (OS), and was significantly associated with the probability of an objective response (7). Axitinib exposure-response analyses showed that AUC at the end of 4 weeks of study treatment was significantly associated with clinical responses (8, 9). Higher axitinib exposure was associated with a higher probability of response, longer progression-free survival (PFS) and OS, and was an independent predictor of survival (9). Additionally, in patients undergoing axitinib dose-titration, higher AUC was associated with a higher probability of response (9). Pazopanib has also demonstrated a relationship between exposure and efficacy in the advanced RCC setting (10). In several studies, the pazopanib efficacy  $C_{\text{trough}}$  threshold associated with significant increases in PFS and tumor shrinkage in advanced RCC was established as 20.5  $\mu\text{g/mL}$ .

In the current analysis, we aimed to characterize the relationship between pazopanib trough concentrations ( $C_{\text{trough}}$ ) and key efficacy endpoint (DFS) and safety endpoints (adverse events [AEs] and AE-related treatment discontinuation).

## **Patients and Methods**

### ***Study design***

Detailed description of the PROTECT study design has been previously reported (4). In summary, 1538 patients with resected nonmetastatic clear cell RCC that was pT2G3-4N0, pT3-T4 G<sub>any</sub>N0, or pT<sub>any</sub>G<sub>any</sub>, N1 (as per tumor, node, metastasis [TNM] classification [AJCC 2010 version] and Fuhrman nuclear grades), were randomly assigned 1:1 to pazopanib or matching placebo for one year. The study was initiated with a starting dose of 800 mg per day, and 198 and 205 patients were assigned to the pazopanib and placebo groups, respectively (ITT800). Due to a higher-than-expected treatment discontinuation rate, a protocol amendment reduced the starting dose to 600 mg per day, and 571 and 564 patients were assigned to pazopanib and placebo, respectively (ITT600). The primary endpoint was amended to investigator-assessed DFS in the ITT600 population; DFS was assessed in the ITT800 population as a secondary endpoint. Safety assessments were conducted on patients randomly assigned to a starting dose of 600 mg or 800 mg who received  $\geq 1$  dose of study treatment. Patients in ITT600 could be maintained at this dose or escalated to 800 mg after 8–12 weeks based on safety and tolerability. Dose reductions in ITT600 and ITT800 were allowed for management of treatment-related toxicity.

Local institutional review boards approved the study. The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki, and all patients provided written informed consent.

### ***Pazopanib exposure in the PROTECT study***

Following the introduction of the 600 mg starting dose, predose blood sampling was performed to determine steady-state pazopanib  $C_{\text{trough}}$ , collected at week 3 or 5 (early  $C_{\text{trough}}$ ) and week 16 or 20 (late  $C_{\text{trough}}$ ). In addition to blood sampling for trough concentrations, serial pharmacokinetic (PK) sampling (3 additional time points) was conducted in 68 pazopanib-treated subjects during weeks 3 or 5 at 1–2 hours, 3–4 hours, and 6–8 hours after administration of study treatment. Pazopanib plasma concentrations were determined via a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method. Briefly, pazopanib and the internal standard (IS) were extracted from samples using protein precipitation in human plasma. The calibration curves were linear over the range of 100 (lower limit of quantification [LLOQ]) to 50000 (upper limit of quantification [ULOQ]) ng/mL in human plasma.

Patients were evaluable for PK analysis if they received  $\geq 1$  dose of pazopanib and had a corresponding PK sample. Predose samples must have been collected before the next pazopanib dose and 20–28 hours after the last dose administration; steady-state samples required at least 10 consecutive daily pazopanib doses without a dose change or interruption. Evaluable steady-state  $C_{\text{trough}}$  was collected from 311 patients at week 3 or 5 and from 250 patients at week 16 or 20.

### ***Population PK analysis***

The pazopanib population PK model was previously developed with historical PK data including 451 subjects (healthy volunteers and cancer patients) and 4011 PK samples (rich/sparse sampling) collected after a single intravenous infusion of 5 mg (7 subjects) and daily oral doses ranging from 50 to 2000 mg (**Supplementary Table S1**). Starting doses of 800, 600, and 400 mg represented 66%, 2.2%, and 13% of historical PK samples, respectively. The pazopanib historical population PK model was a two-compartment disposition model with delayed first-

order absorption and first-order elimination including an oral bioavailability decreasing with dose and time (11).

The historical population PK model was used to compute empirical Bayes estimates (EBEs) of pazopanib plasma concentrations for each patient having evaluable PK samples in the PROTECT study given their actual dosing/sampling time and covariate data. The predicted and observed pazopanib plasma concentrations for the PROTECT study were compared by visual inspection of diagnostic plots (prediction-corrected visual predictive check, normalized prediction distribution errors, observed vs predicted concentrations). If the historical population PK model was inadequate to describe PK data in the PROTECT study (suggesting different PK properties in the adjuvant population), then model parameters were re-estimated using a dataset containing both historical and PROTECT PK data, which included a covariate effect for the PROTECT population to quantify any deviation from historical data. The final population PK model was used to simulate steady-state exposure metrics (area under the curve from 0 to 24 hours [ $AUC_{0-24h,ss}$ ], maximum concentration [ $C_{max,ss}$ ], and  $C_{trough,ss}$ ) for continuous daily oral doses of 200, 400, 600 or 800 mg. Model parameters were estimated by a nonlinear mixed effect modeling approach using Monolix 4.3.2.

### ***Exposure/dose-efficacy analyses***

The relationship between  $C_{trough}$  and DFS was evaluated using Kaplan-Meier curves of DFS by early and late  $C_{trough}$  quartiles. Furthermore, a multivariate Cox proportional hazard regression analysis for DFS using TNM staging, Fuhrman nuclear grade, and both early and late  $C_{trough}$  as covariates was performed. A similar Cox proportional hazard regression analysis for DFS using TNM staging, Fuhrman nuclear grade, and either early or late  $C_{trough}$  was also performed. DFS

was compared in patients with early and late  $C_{\text{trough}} \leq 20.5$  or  $>20.5$   $\mu\text{g/mL}$ , which is the threshold for pazopanib  $C_{\text{trough}}$  associated with longer PFS and higher tumor shrinkage in advanced RCC (10). Kaplan-Meier curves were used to plot DFS by  $>$  or  $\leq$  median dose intensity up to week 8 to investigate the potential effect of the starting dose on DFS.

### ***Exposure-safety analyses***

Exposure-safety relationships were investigated between early  $C_{\text{trough}}$  and the proportion of AEs of interest based on pazopanib's known safety profile that was reported within the first 12 weeks of treatment, and between late  $C_{\text{trough}}$  and the proportion of AEs occurring later than 12 weeks up to the date of last dose (+28 days). The AEs analyzed included increased alanine aminotransferase (ALT), diarrhea, hypertension, hand-foot syndrome, stomatitis, and cytopenia (thrombocytopenia and leukopenia/neutropenia). The effect of pazopanib exposure on AE-related treatment discontinuations was investigated by comparing the percentage of patients with AE-related treatment discontinuations across  $C_{\text{trough}}$  quartiles.

## **Results**

### ***Pazopanib PK exposure in the PROTECT study***

A total of 311 and 250 patients had evaluable samples for early and late  $C_{\text{trough}}$  measurements, respectively. Most patients with available  $C_{\text{trough}}$  samples ( $>90\%$ ) were in the ITT600 group. Among patients in ITT600, 118 (21%) had a protocol-defined dose escalation by week 12. **Table 1** summarizes early and late  $C_{\text{trough}}$  by pazopanib steady-state dose.  $C_{\text{trough}}$  values were assigned to a steady-state dose if 10 consecutive doses without dose modifications or interruptions were

administered prior to sampling. The geometric mean (geometric coefficient of variation [CV%]) of the early  $C_{\text{trough}}$  at 600 mg was 31.4  $\mu\text{g/mL}$  (56.7%); few early  $C_{\text{trough}}$  samples were collected at steady-state doses of 800 mg or 400 mg given that most patients were on the starting dose of 600 mg at the time of PK sample collection, i.e. Week 3 or 5. Early  $C_{\text{trough}}$  overlapped across dose levels. Because dose escalations (from 600 mg to 800 mg after 8 to 12 weeks based on subject's tolerability) and dose reductions (from 600 mg to 400 mg to manage treatment-related toxicity) were allowed, a greater proportion of late  $C_{\text{trough}}$  samples were obtained during treatment with 800 mg and 400 mg compared with early  $C_{\text{trough}}$ . The geometric mean late  $C_{\text{trough}}$  overlapped across dose levels, and pazopanib exposure was variable, ranging from 23.2  $\mu\text{g/mL}$  to 28.6  $\mu\text{g/mL}$ , with geometric mean CV% for  $C_{\text{trough}}$  ranging from 56.7% to 70.6% across dose levels (**Table 1**). The quartiles for pazopanib early and late  $C_{\text{trough}}$  are presented in

**Supplementary Table S2.**

### *Exposure-efficacy analyses*

Longer DFS was observed in patients achieving higher early  $C_{\text{trough}}$  quartiles (**Figure 1**). For late  $C_{\text{trough}}$ , patients in the upper 3 quartiles (Q2 to Q4) trended towards longer DFS compared with the lowest quartile (Q1). In the multivariate Cox regression analysis with both early and late  $C_{\text{trough}}$ , early  $C_{\text{trough}}$  was a significant covariate for DFS (hazard ratio [HR], 0.58; 95% CI, 0.42–0.82;  $P = 0.002$ ), indicating a correlation between early  $C_{\text{trough}}$  and pazopanib efficacy. To evaluate the independent association of early and late PK exposure with DFS and given the correlation between early  $C_{\text{trough}}$  and late  $C_{\text{trough}}$  (Pearson correlation coefficient = 0.45), two separate Cox regression models were evaluated. The multivariate analysis between DFS and

either early or late  $C_{\text{trough}}$  showed both exposure metrics to be significant covariates for DFS ( $P = 0.000758$  and  $0.000496$  for early and late  $C_{\text{trough}}$ , respectively).

The threshold  $C_{\text{trough}}$  associated with increased PFS and tumor shrinkage in advanced RCC patients,  $>20.5 \mu\text{g/mL}$  (10), was achieved by 82% and 75% of patients for early and late  $C_{\text{trough}}$ , respectively. A significantly longer DFS was observed in patients achieving early or late  $C_{\text{trough}} >20.5 \mu\text{g/mL}$  (**Figure 1**).

### *Dose-efficacy analyses*

The median dose intensity across the entire treatment period was 593.7 mg in the 600 mg and 648.4 mg in the 800 mg dose cohorts. The mean pazopanib daily dose (dose intensity) decreased in both cohorts during the first ~8 weeks of treatment. Dose intensity increased between weeks 8 and 12 in the 600 mg dose cohort, and from week 12 remained ~550 mg in the 600 mg dose cohort and ~600 mg in the 800 mg dose cohort (**Figure 2**). The main difference in dose intensity between the two dose cohorts appeared during the initial phase of treatment (in the first 8 to 12 weeks) (**Figure 2**). Thus, the median dose intensity up to week 8, determined to be 600 mg, was used as a cutoff to explore the relationship between DFS and pazopanib starting dose. No relationship was observed between DFS and dose intensity up to week 8 when using this median cut-off (**Figure 2**).

### *Exposure-safety analyses*

The proportion of patients with AE-related discontinuations was similar across early  $C_{\text{trough}}$  quartiles (**Table 2**). There was a concentration-dependent relationship between pazopanib early

$C_{\text{trough}}$  and the proportion of all-grade AEs during the first 12 weeks of treatment (**Figure 3A**). No clear relationship was observed between early  $C_{\text{trough}}$  and the proportion of grade 3/4 AEs during the first 12 weeks of treatment, with the exception of hypertension (**Figure 3B**). There was no apparent relationship between late  $C_{\text{trough}}$  and the proportion of all-grade or grade 3/4 AEs occurring later than 12 weeks up to the date of last dose (+28 days) (**Figure 4**).

### ***Population PK analysis***

The PROTECT population PK dataset comprised 537 patients and 1079 PK samples collected at 600 mg (69%), 400 mg (16%), 800 mg (13%) and 200 mg (2%). Pazopanib exposure in the PROTECT study was not properly described by the historical population PK model.  $C_{\text{trough}}$  and  $C_{\text{max}}$  were under-predicted by about 30%, suggesting a higher oral bioavailability in PROTECT patients despite comparable patient characteristics for most of the explored covariates between PROTECT and historical populations (**Supplementary Table S3**). Nevertheless, a greater proportion of historical patients had a lower Eastern Cooperative Oncology Group performance status compared with PROTECT patients (36.6% vs. 5.40%), which would be expected in the advanced/metastatic disease setting.

Therefore, model parameters were re-estimated using a combined dataset of historical and PROTECT data. Including a covariate effect on oral bioavailability for the PROTECT population led to adequate description of pazopanib  $C_{\text{trough}}$  and  $C_{\text{max}}$  when considering a 30% higher exposure compared with the historical population. Inspection of prediction-corrected visual predictive check plots revealed good agreement between median observed  $C_{\text{trough}}$  and the 90% prediction interval of simulated median  $C_{\text{trough}}$ , confirming the final model was appropriate to describe pazopanib PKs in the PROTECT study (**Supplementary Figure S1**). Final parameter

estimates are shown in **Supplementary Table S4**. All model parameters were estimated with good precision (% relative standard error < 12%). Inter-subject variability was high on absorption parameters (73–92%) and less pronounced on clearance (~ 50–60%). Absolute oral bioavailability was estimated at 21% after repeated administration of 800 mg, to be 40% higher at 400 mg than 800 mg, and 30% lower at steady state than after single administration. Co-administration with food was estimated to decrease the absorption rate constant by 62% and to increase oral bioavailability by 2.3- and 2.9-fold after a single administration of 400 and 800 mg, respectively. Co-administration of gastric pH-elevating agents led to a 12% decrease of pazopanib oral bioavailability and was considered clinically not relevant.

Because of the limited early  $C_{\text{trough}}$  samples available at the 800 mg dose (n=7), a population PK model-based simulation was used to explore the impact of dose and patient population (historical vs. PROTECT) on pazopanib PKs by deriving steady-state exposure metrics ( $AUC_{0-24h,ss}$ ;  $C_{\text{max},ss}$ ;  $C_{\text{trough},ss}$ ) under the fasted state. The comparison of simulated steady-state exposure metrics by week 4 across dose levels (200 mg to 800 mg) and patient population (historical vs. PROTECT) is shown in **Supplementary Figure S2**. Simulated mean values of exposure metrics at steady state obtained after 800 mg were less than 2.5 fold higher compared with values after 200 mg, reflecting the dose-dependent exposure of pazopanib driven by solubility-limited absorption. Simulated mean values of steady-state exposure metrics were on average 25% higher after 600 mg and 30% higher after 800 mg in PROTECT compared with historical pazopanib trials. In the PROTECT population, the simulated values of steady-state exposure metrics were on average only 17% higher at 800 mg compared with 600 mg.

## Discussion

The exposure response analysis presented in the current report from the PROTECT study, primarily based on data from patients starting pazopanib at 600 mg, indicated a correlation between higher early  $C_{\text{trough}}$  and longer DFS. Patients who achieved early or late  $C_{\text{trough}} >20.5$   $\mu\text{g/mL}$ , the efficacy threshold identified for advanced RCC (10), had longer DFS than patients with  $C_{\text{trough}} \leq 20.5$   $\mu\text{g/mL}$ . Dose intensity in the first 8 weeks in PROTECT was not correlated to DFS, suggesting that a higher pazopanib starting dose does not explain the favorable reduction in the relative risk of relapse achieved in ITT800. Therefore, the current exposure-response analysis suggests that some patients achieve higher pazopanib  $C_{\text{trough}}$ , which is associated with improved DFS, regardless of whether the starting dose was 600 mg or 800 mg, and regardless of subsequent dose reduction. This finding is consistent with the exposure-response relationships for pazopanib, sunitinib, and axitinib in the advanced/metastatic RCC setting where clinical outcome was correlated to higher PK exposure (7-10). Further clinical testing could be warranted to identify and confirm specific target thresholds for VEGF-TKIs, which may help guide PK-guided dosing vs standard VEGF-TKIs treatment. It is important to highlight that at this point, the available data does not support VEGF-TKIs treatment discontinuation for patients with a  $C_{\text{trough}}$  below a certain threshold if they are still achieving clinical benefit from treatment. The minor role of pazopanib starting dose on clinical outcome is supported by the solubility-limited absorption of pazopanib, the high inter-individual variability in pazopanib exposure (~60-70%), the overlapping pazopanib exposure between 600 and 800 mg as predicted by the population PK model simulations as well as the similar DFS rates at yearly time points between pazopanib-treated patients in ITT800 and ITT600 (4). Our finding that pazopanib  $C_{\text{trough}}$  exposure, but not pazopanib prescribing dose, is crucial for improved DFS in the adjuvant setting in RCC patients,

could be the primary driver of discrepancies in outcomes of the recent adjuvant VEGF-TKI trials (2-4).

Two other phase III studies evaluating the efficacy and safety of VEGFR-TKIs in the adjuvant RCC setting have recently been reported (2, 3). Adjuvant sunitinib in the S-TRAC study demonstrated a statistically significant improvement in DFS over placebo ( $P = 0.03$ ) (3). The starting dose in this study was maintained at the same schedule approved in advanced RCC (50 mg daily on a 4-week on/2-week off schedule). In the ASSURE study, neither sunitinib nor sorafenib improved DFS compared to placebo (2). However, in contrast to S-TRAC and similar to PROTECT, a reduced starting dose was implemented partway through the ASSURE study to reduce treatment-related discontinuations (2). This pattern could be mistakenly perceived as if the higher starting dose explains a primary cause for the disparate outcome between adjuvant trials. However, sub-analyses of ASSURE suggest an absence of treatment effect in both patients starting at the full and reduced doses (12). Consistent with findings from PROTECT, quartiles of dose intensity per cycle did not correlate with DFS for either sunitinib or sorafenib in a subanalysis of high-risk clear cell RCC patients in ASSURE (12). These results suggest that a higher starting dose may not be the primary driver for the disparate outcome across adjuvant RCC trials. However, given the high inter-patient variability in VEGF-TKIs exposure and the overlapping exposure expected from the lower and higher doses tested (for example, only 17% higher pazopanib exposure from the 800 mg vs 600 mg dose), the disparate outcomes could be simply due to different exposure levels in different trials. For example, pazopanib exposure was 25%-30% higher in PROTECT compared with historical pazopanib trials despite comparable patient characteristics for most of the explored covariates in both PROTECT and historical populations. The underlying cause for higher pazopanib exposure in PROTECT is not clearly

understood. To our knowledge, neither S-TRAC nor ASSURE trials collected PK data and therefore, the exposure levels in these trials are unknown. Further clinical testing could be warranted to understand sunitinib exposure levels in the adjuvant setting.

In PROTECT, higher early  $C_{\text{trough}}$  was associated with a greater proportion of all-grade AEs during the first 12 weeks. Mild adverse events (grade 1 and 2) usually do not meet the protocol-defined discontinuation criteria, and therefore are unlikely to result in a difference in discontinuation rate. Despite the relationship observed between  $C_{\text{trough}}$  and the proportion of all-grade AEs, the proportion of on-treatment mild toxicities (grade 1/2) was similar overall in the 2 dose groups (33% and 38% in the 800 mg and 600 mg groups, respectively), suggesting that the higher dose is not associated with an increase in the proportion of mild adverse events. The higher-dose group was associated with slightly higher grade 3/4 toxicity (66% vs 59% in the 800 mg group and the 600 mg, respectively). The difference in grade 3/4 toxicity did not translate into a higher discontinuation rate (39% vs 35% in the 800 mg group and the 600 mg, respectively) (4). Furthermore, patients in both dose groups had a similar time on study drug—52% by month 9 and 49% by month 12. The similar proportion of all-grade AEs, grade 3/4 safety profile, and time on study treatment in the two dose groups is consistent with the overlapping exposure expected due to the solubility-limited bioavailability of pazopanib (steady-state exposure only 17% higher at 800 mg compared with 600 mg).

However, there was no correlation between  $C_{\text{trough}}$  and the proportion of grade 3/4 AEs or AE-related treatment discontinuations, with the exception of grade 3/4 hypertension. The increased proportion of grade 3/4 hypertension with increasing  $C_{\text{trough}}$  observed in PROTECT is consistent with results from a phase II study in advanced RCC (10). Hypertension is a common on-target AE with VEGFR-TKIs (13,14), and is well managed by dose reduction/interruption and/or

treatment with anti-hypertensive agents (15). Only 3% of patients permanently discontinued pazopanib due to hypertension in the 600 and 800 mg cohorts in PROTECT (4), suggesting that hypertension was clinically well managed in this study.

At the time of the blinded aggregate safety review, ALT elevation was the most common single AE leading to withdrawal of study treatment and was one of the main drivers in reducing the starting dose during the study from 800 mg to 600 mg. The exposure-safety analysis did not reveal a clear relationship between pazopanib exposure and ALT elevation. This is in line with the similar percentage of all-grade ALT increased (35% and 33%) and treatment discontinuation due to ALT elevation (16% and 18%) in the Safety<sub>600mg</sub> and Safety<sub>800mg</sub> populations, respectively (4). A phase II study in advanced RCC similarly found no relationship between grade 3/4 increased ALT and pazopanib exposure, as suggested by the same percentage (4%) of increased ALT in both upper and lower C<sub>trough</sub> quartiles in this study (10).

The PKs of pazopanib in PROTECT patients was adequately described by a two-compartment disposition model with delayed first order absorption and first-order elimination, including an oral bioavailability decreasing with dose and time. The current population PK analysis revealed dose-dependent PKs for pazopanib, which is in agreement with the dose-escalation study [VEG10003] reporting an increase of C<sub>max</sub> and AUC<sub>0-24h</sub> in a less than dose-proportional fashion over the range of 50 mg to 2000 mg, reaching a plateau for doses above 800 mg (16). This suggests absorption is limited by pazopanib's low solubility. Population PK model-based simulations showed that steady-state exposure metrics were on average only 17% higher at 800 mg compared with 600 mg.

The current population PK analysis suggests time-dependent PKs of pazopanib. Indeed, the oral bioavailability was estimated to be 30% lower at steady state than after single administration.

There is no strong evidence supporting this result, but pazopanib is a substrate of efflux transporters (P-gp, BCRP) and mainly metabolized by CYP3A4 enzymes. Therefore, it can be speculated that auto-induction of those transporters and/or CYP3A4 enzymes may decrease over time the fraction of dose reaching the systemic circulation (i.e., reducing the fraction absorbed and/or increasing the first pass effect).

The observed early  $C_{\text{trough}}$  in PROTECT was under-predicted by ~30% compared with the historical population PK model, suggesting higher pazopanib exposure in PROTECT despite comparable patient characteristics for most of the explored covariates in both PROTECT and historical populations. Inclusion of a covariate effect on pazopanib oral bioavailability for the PROTECT population led to adequate description of pazopanib exposure confirming a 30% higher exposure in the PROTECT study compared with historical PK data. Nevertheless, the underlying cause for higher pazopanib exposure in PROTECT is not clearly understood. Future clinical studies aiming to identify genotypes or other biomarkers associated with improved pazopanib exposure may allow the identification of patient subgroups more likely to benefit from adjuvant pazopanib therapy.

## Conclusions

This exposure-response analysis of patients primarily treated with the starting dose of 600 mg daily pazopanib found that higher exposure ( $C_{\text{trough}}$ ) was associated with improved DFS in the adjuvant RCC setting. Patients with  $C_{\text{trough}}$  (early or late)  $>20.5 \mu\text{g/mL}$  achieved longer DFS. This suggests that patients achieving higher pazopanib  $C_{\text{trough}}$  derived more clinical benefit from adjuvant pazopanib therapy. This implies that potential benefit to adjuvant therapy is driven by a pharmacodynamic benefit rather than by dose. Furthermore, pazopanib exposure was not

associated with dose, which is unsurprising given the non-linear PK of pazopanib and pronounced inter-subject variability in pazopanib exposure. Grade 3/4 AEs and AE-related discontinuations did not correlate with pazopanib exposure, except for grade 3/4 hypertension, which was clinically well managed.

### **Author Contributions**

**Conception and design:** C. N. Sternberg, N. B. Haas, R. J. Motzer, P. Russo

**Data acquisition:** C. N. Sternberg, N. B. Haas, R. J. Motzer, F. Donskov, M. Elmeliegy, C. Doehn, P. Russo

**Collection and assembly of data:** C. N. Sternberg, M. Elmeliegy, C. Doehn, P. Russo

**Data analysis and interpretation:** C. N. Sternberg, N. B. Haas, R. J. Motzer, F. Donskov, M. Elmeliegy, H. Banerjee, C. Doehn, G. Baneyx, P. Russo

**Writing, review and/or revision of the manuscript:** C. N. Sternberg, N. B. Haas, R. J. Motzer, F. Donskov, H. Banerjee, M. Elmeliegy, C. Doehn, G. Baneyx, P. Russo

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**Table 1.** C<sub>trough</sub> by dose level in PROTECT<sup>a</sup>

Scheduled sampling time point	Statistic	Pazopanib actual dose		
		400 mg	600 mg	800 mg
Week 3 or 5 (early C <sub>trough</sub> )	Total number of samples	20	288	7
	Evaluable samples	20	285	6
	Mean, µg/mL (SD)	40.8 (15.6)	34.8 (15.4)	34.5 (22.2)
	CV%	38.2	44.3	64.4
	Geometric mean (CV%)	36.4 (61.0)	31.4 (56.7)	35.3 (70.6)
	Median, µg/mL (range)	46.6 (6.6, 67.8)	34.3 (0.0, 8.6)	37.0 (0.0, 62.6)
Week 16 or 20 (late C <sub>trough</sub> )	Total number of samples	73	94	88
	Evaluable samples	71	93	86
	Mean, µg/mL (SD)	27.9 (13.0)	28.9 (14.2)	31.8 (15.9)
	CV%	46.7	49.0	50.0
	Geometric mean (CV%)	23.2 (116.1)	25.3 (69.9)	28.6 (62.6)
	Median, µg/mL (range)	28.2 (0.0, 55.9)	28.8 (0.0, 75.6)	29.7 (0.0, 83.2)

<sup>a</sup>A PK sample was assigned to a dose level if 10 consecutive doses without dose modification or interruption were administered prior to sampling. Most early C<sub>trough</sub> samples were collected during treatment with 600 mg, but because dose escalations (from 600 mg to 800 mg after 8–12 weeks) and dose reductions were allowed, a greater proportion of late C<sub>trough</sub> samples were obtained at the 400 mg and 800 mg doses compared with early C<sub>trough</sub>.

Abbreviations: CV, coefficient of variation; PK, pharmacokinetic; SD, standard deviation.

**Table 2.** AE-related treatment discontinuations by early C<sub>trough</sub> quartiles

<b>Quartile</b>	<b>AE-related treatment discontinuations, %</b>
Q1	26.0
Q2	26.9
Q3	34.6
Q4	28.6

Abbreviations: AE, adverse event; Q, quartile.

## Figure legends

**Figure 1.** Relationship between pazopanib  $C_{\text{trough}}$  and DFS is plotted by early (**A**) and late (**B**)  $C_{\text{trough}}$  quartiles, and using the 20.5  $\mu\text{g/mL}$  cut-off for early (**C**) and late (**D**)  $C_{\text{trough}}$

Abbreviations: CI, confidence interval;  $C_{\text{trough}}$ , trough concentration; DFS, disease-free survival; HR, hazard ratio; NE, not estimable.

**Figure 2.** Mean pazopanib daily dose (dose intensity) over time (**A**) and dose intensity by DFS up to week 8 (**B**).

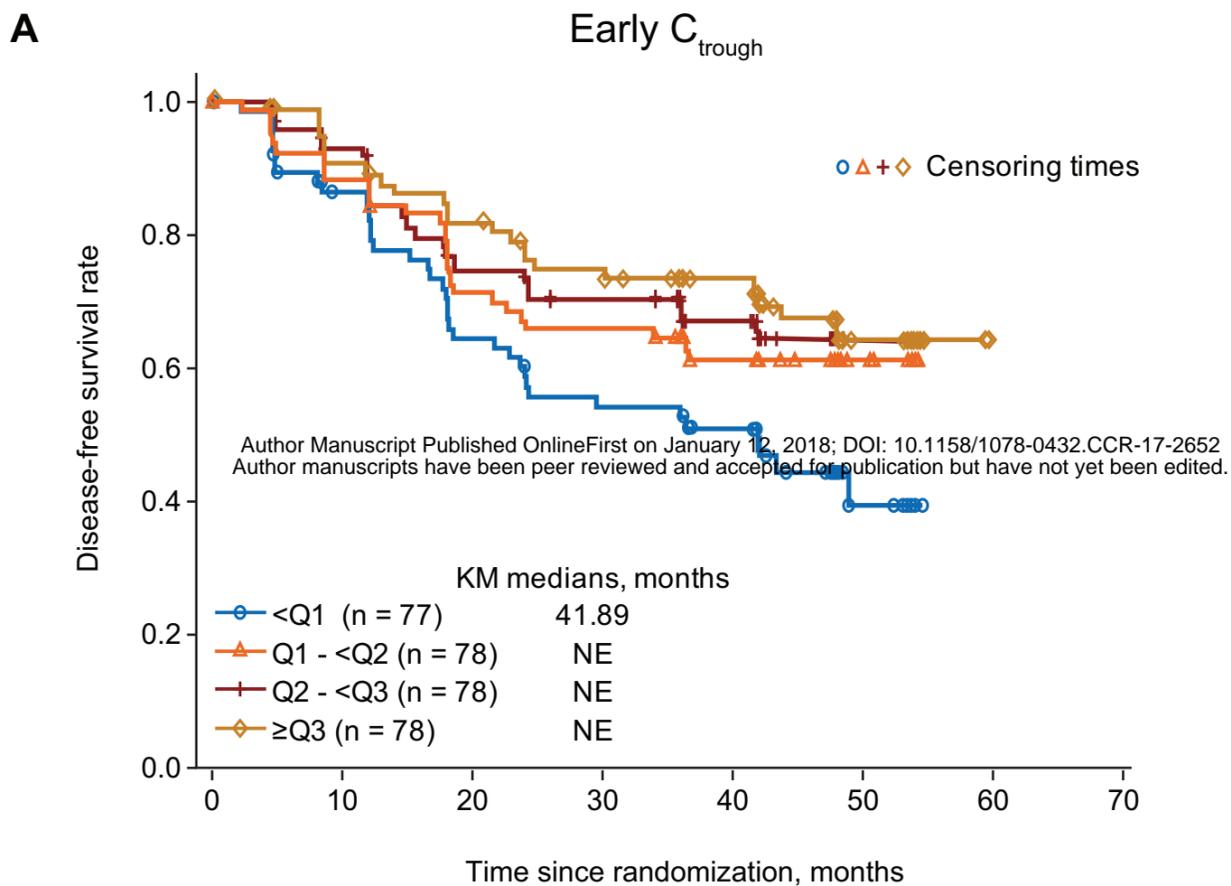
Abbreviations: DFS, disease-free survival; NE, not estimable.

**Figure 3.** Percentage of all-grade (**A**) and grade 3/4 (**B**) adverse events of interest based on pazopanib's known safety profile during the first 12 weeks of treatment by pazopanib early  $C_{\text{trough}}$  quartiles. The number of patients within each quartile are shown in the figure; each patient had one evaluable  $C_{\text{trough}}$  measurement.

Abbreviation: AEs, adverse events;  $C_{\text{trough}}$ , trough concentrations; Q, quartile.

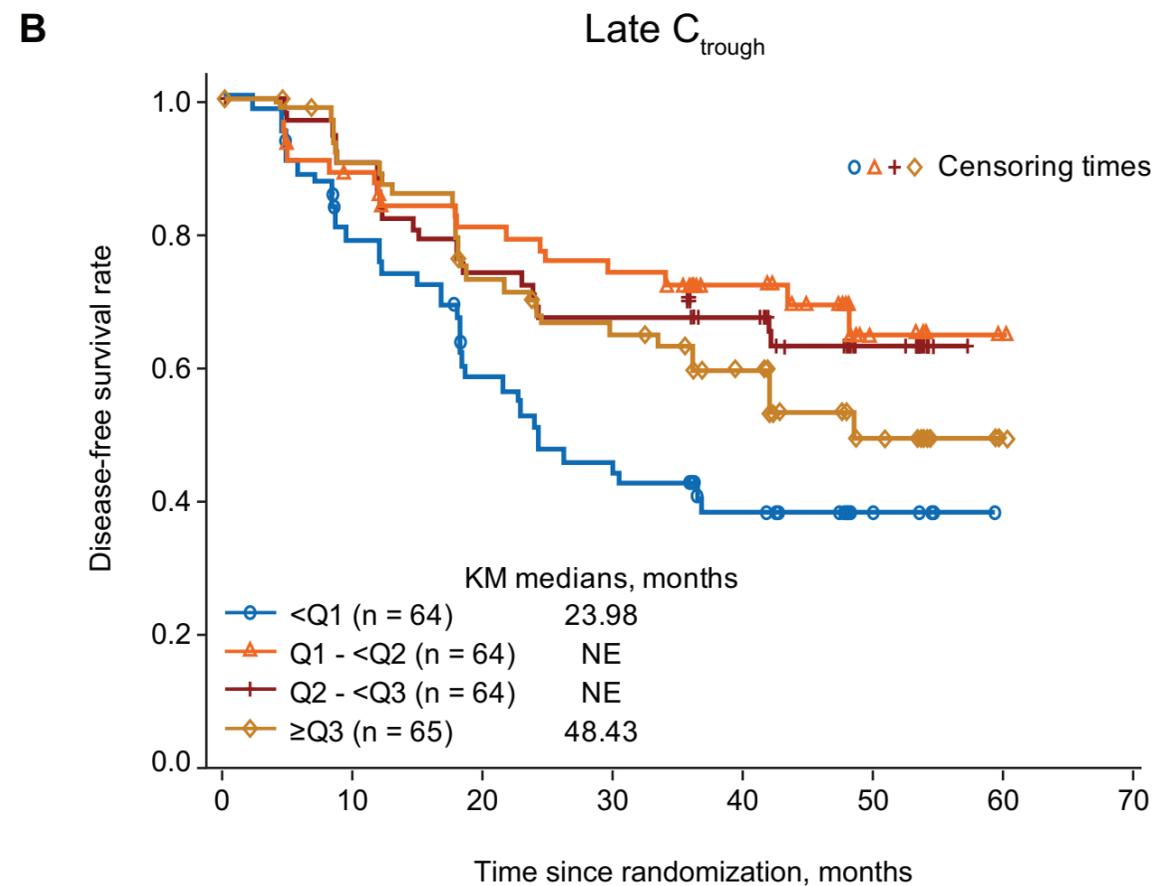
**Figure 4.** Percentage of selected all-grade (A) and grade 3/4 (B) adverse events after week 12 up to last date of dose (+28 days) by pazopanib late  $C_{\text{trough}}$  quartiles. The number of patients within each quartile are shown in the figure; each patient had one evaluable  $C_{\text{trough}}$  measurement.

Abbreviation: AEs, adverse events;  $C_{\text{trough}}$ , trough concentration; Q, quartile.



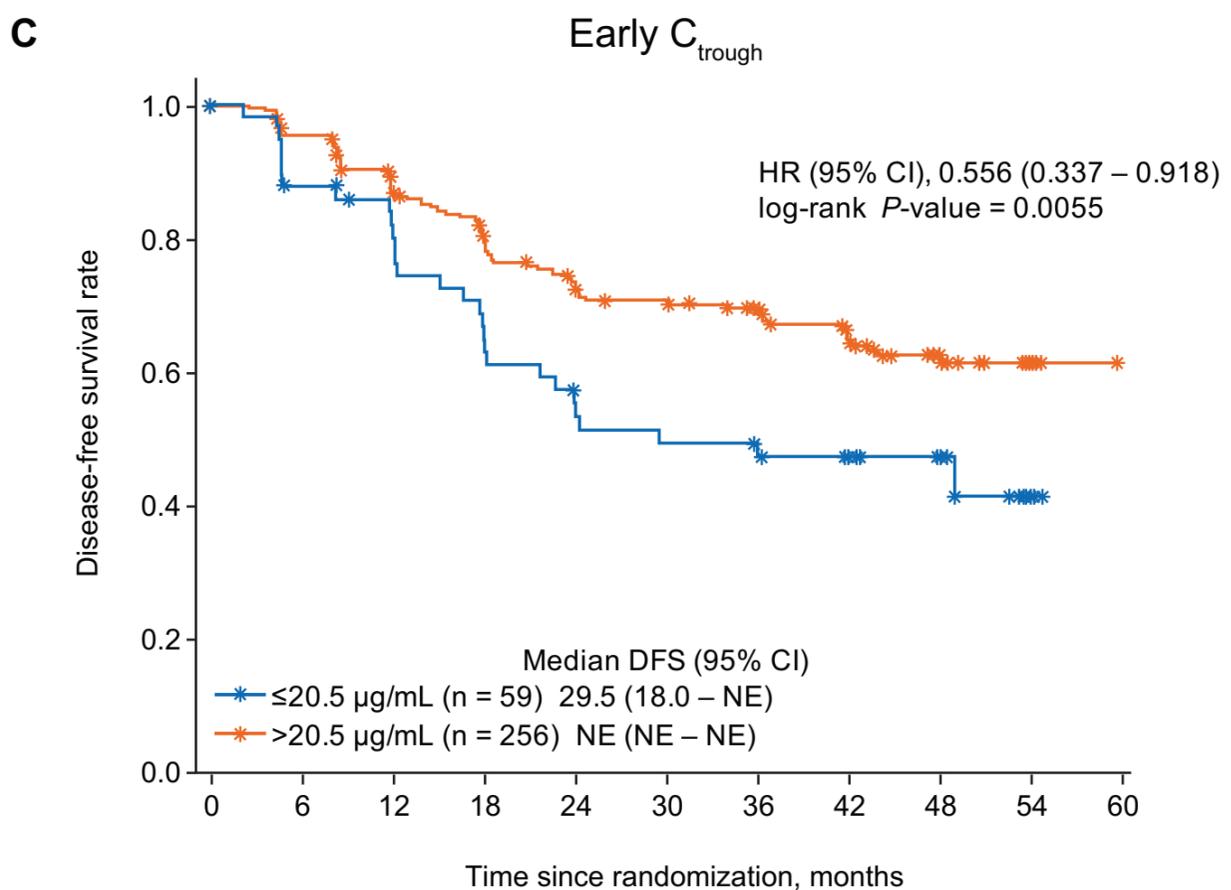
Patients at risk

<Q1	77	59	44	36	30	7	0
Q1 - <Q2	78	68	53	49	37	13	0
Q2 - <Q3	78	65	49	44	32	4	0
≥Q3	78	65	58	51	41	18	0



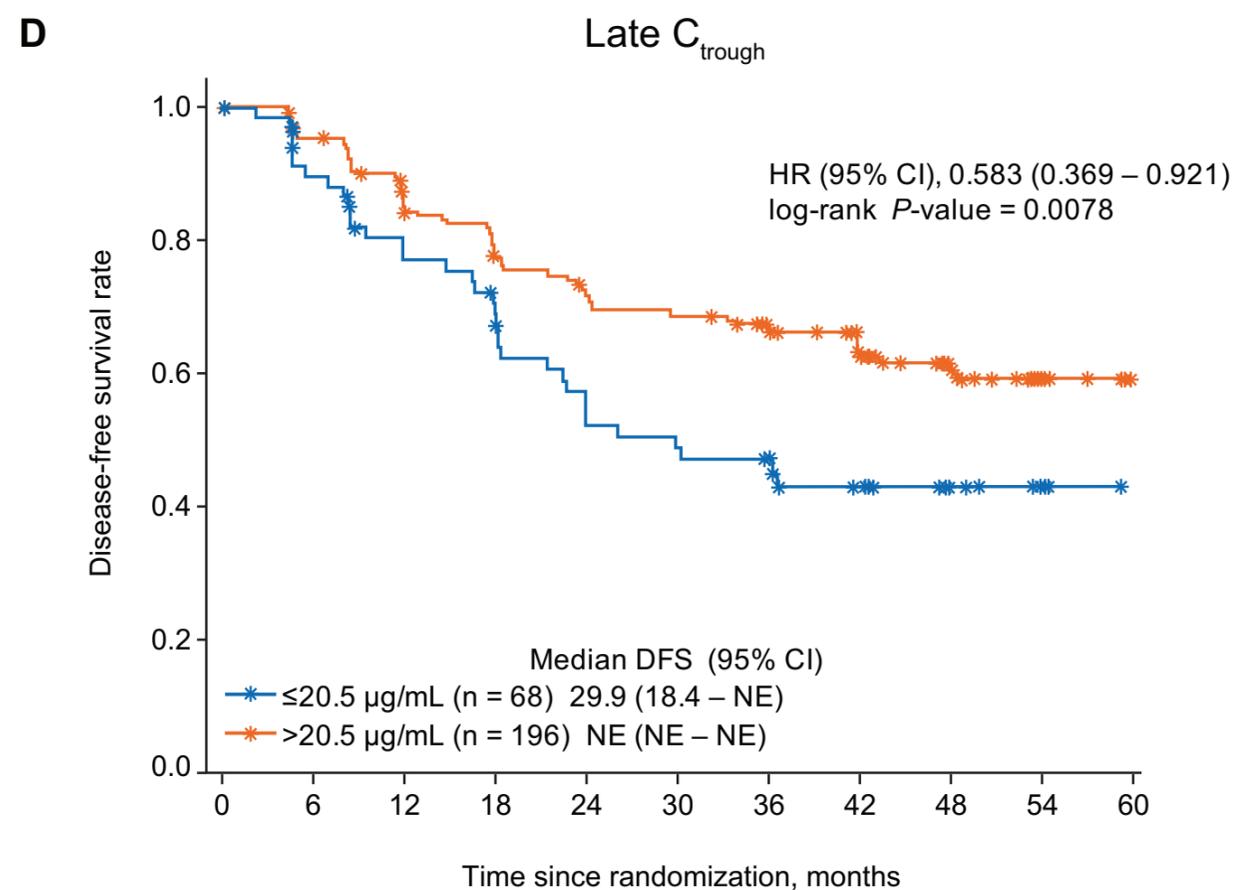
Patients at risk

<Q1	64	47	33	25	17	5	0
Q1 - <Q2	64	55	48	44	32	8	1
Q2 - <Q3	64	56	45	41	35	18	0
≥Q3	65	57	45	39	31	10	1



Patients at risk

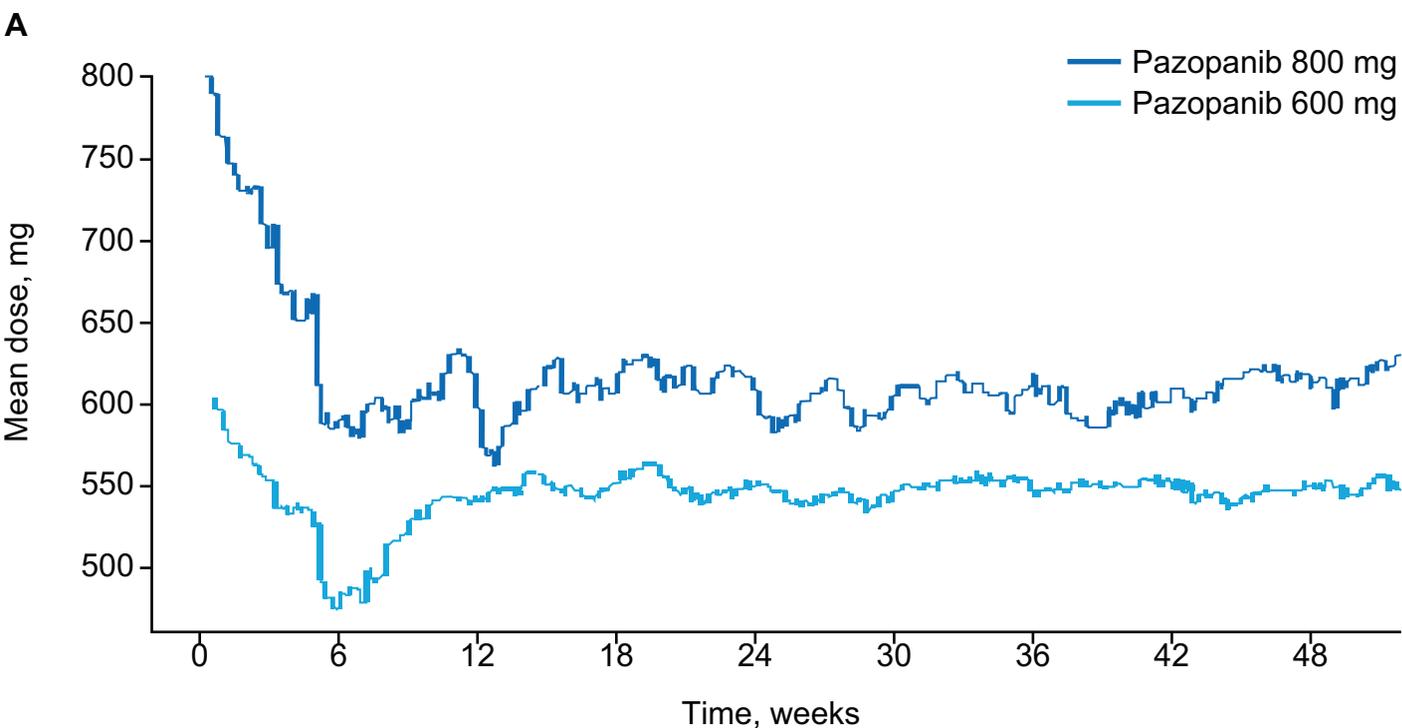
≤20.5 µg/mL	59	49	42	34	27	25	23	17	9	2	0
>20.5 µg/mL	256	231	204	184	164	159	140	96	53	16	0



Patients at risk

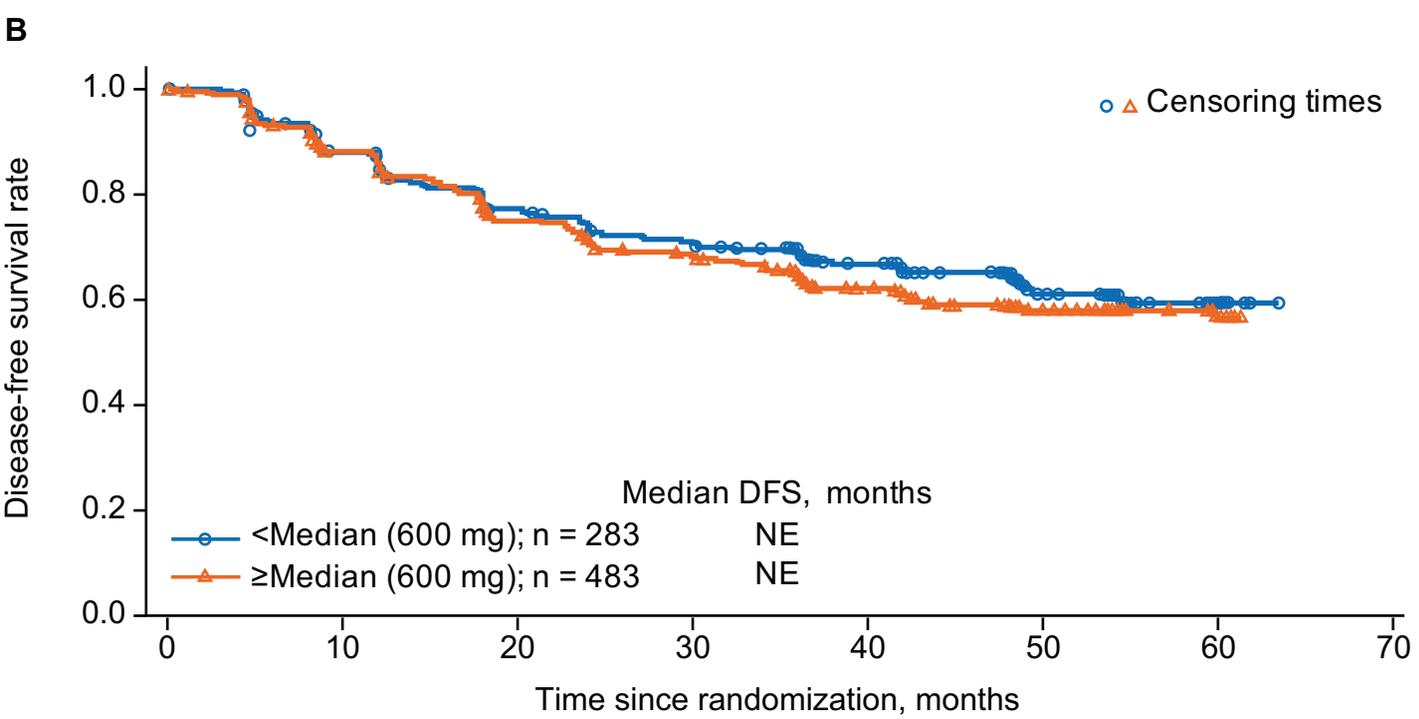
≤20.5 µg/mL	68	60	48	42	31	29	26	19	9	4	0
>20.5 µg/mL	196	183	159	143	132	126	113	83	53	20	3

Figure 2



Number of patients

198	156	134	124	117	113	106	101	98
568	455	408	374	340	321	311	293	279



Patients at risk

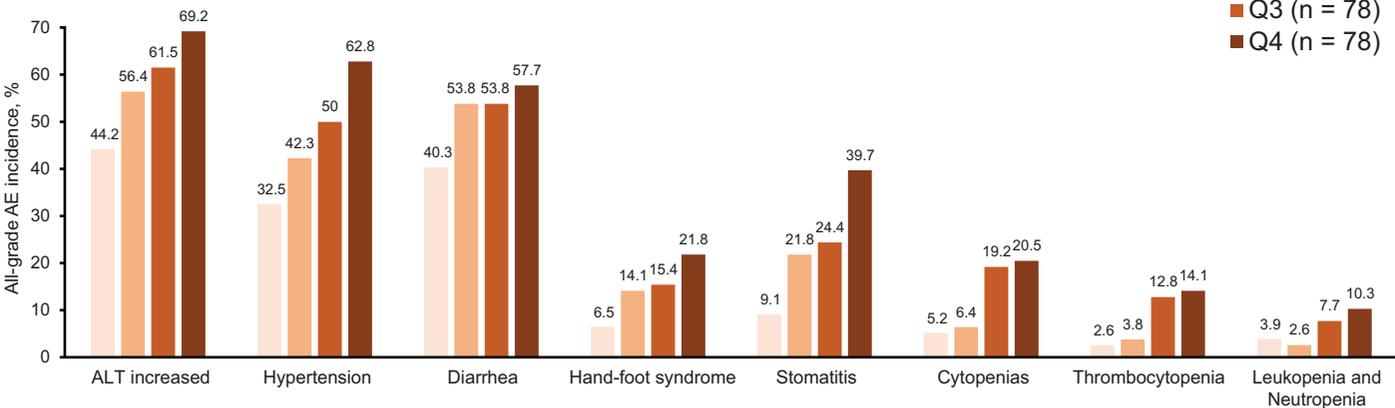
<Median	77	230	193	172	137	61	12	0
≥Median	78	378	315	282	210	100	30	0

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A

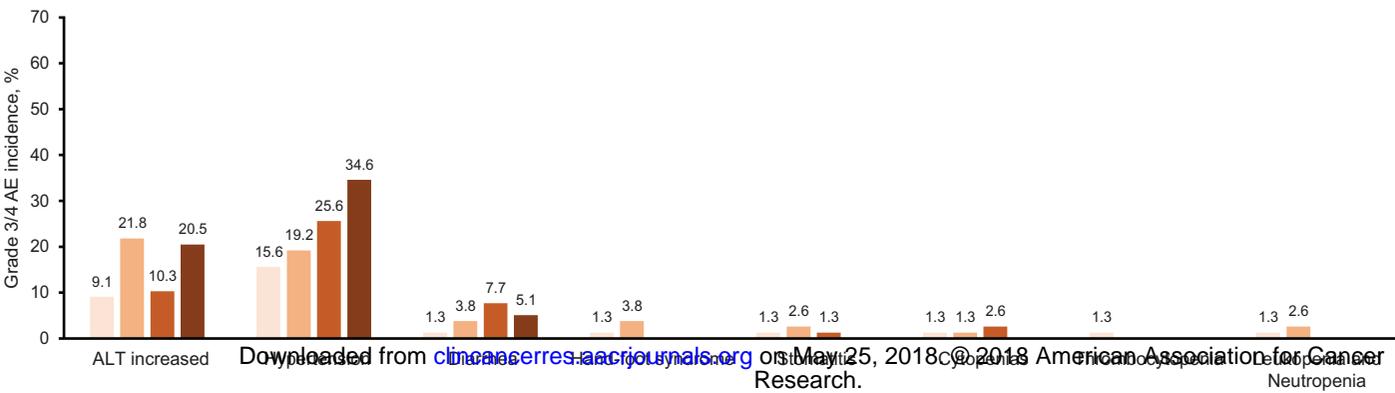
## All-grade AEs

Q1 (n = 77)  
Q2 (n = 78)  
Q3 (n = 78)  
Q4 (n = 78)



B

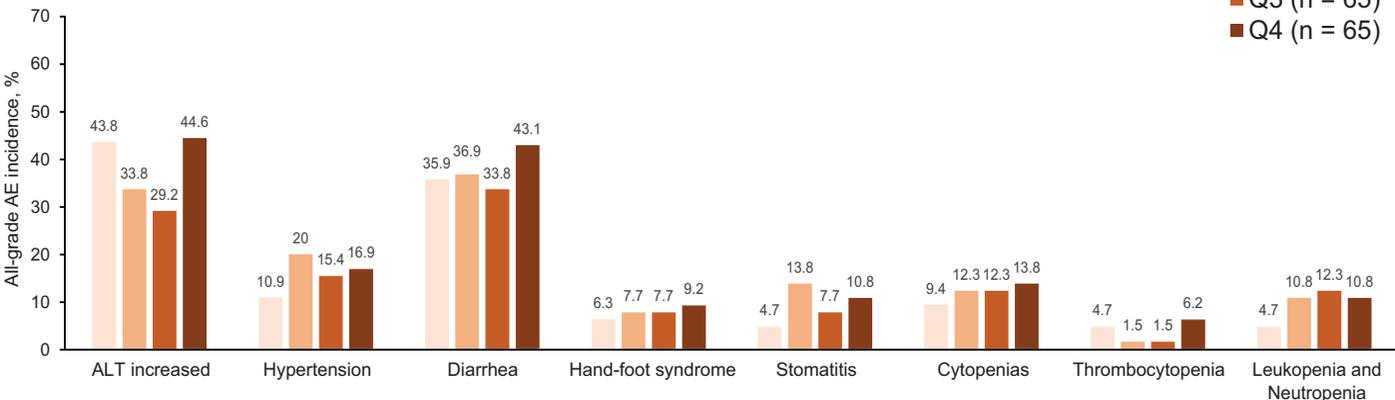
## Grade 3/4 AEs



A

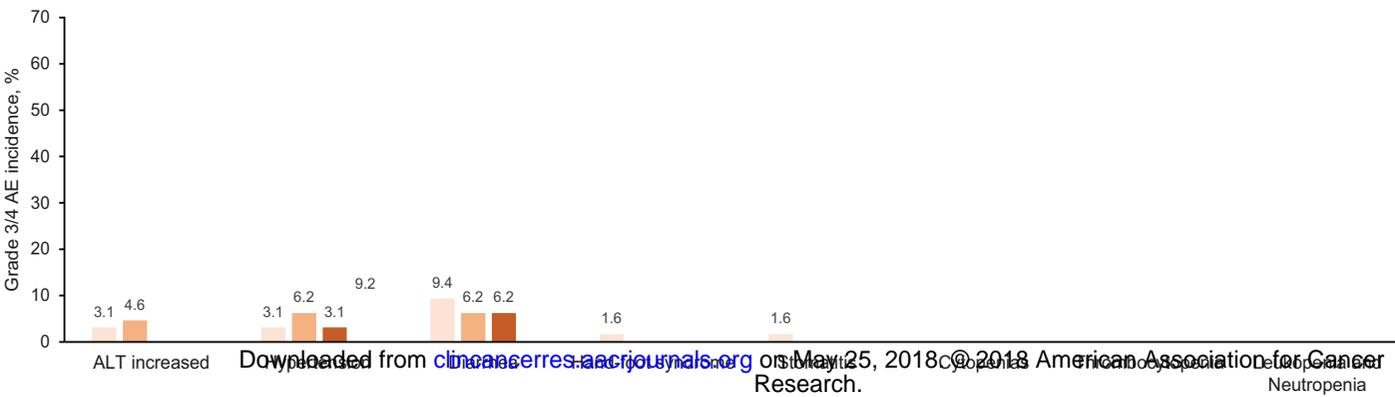
## All-grade AEs

Q1 (n = 64)  
Q2 (n = 65)  
Q3 (n = 65)  
Q4 (n = 65)



B

## Grade 3/4 AEs



# Clinical Cancer Research

## Pazopanib Exposure Relationship with Clinical Efficacy and Safety in the Adjuvant Treatment of Advanced Renal Cell Carcinoma

Cora Sternberg, Frede Donskov, Naomi B. Haas, et al.

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