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COMPARZ Post Hoc Analysis: Characterizing Pazopanib Responders With Advanced Renal Cell Carcinoma

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Study data are available upon reasonable request to Jackie Han at jackie.han@novartis.com.

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Supplemental Data

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Abstract

This post hoc analysis of the COMPARZ study (pazopanib, n = 557; sunitinib, n = 553) supported similar efficacy of first-line pazopanib and first-line sunitinib treatment in advanced renal cell carcinoma. Patients who required dose modifications because of toxicity received higher cumulative doses with longer time of treatment and had significantly better objective response rate, progression-free survival, and overall survival than patients with minimal toxicity.

Background: The phase III COMPARZ study showed noninferior efficacy of pazopanib versus sunitinib in advanced renal cell carcinoma. In this COMPARZ post hoc analysis we characterized pazopanib responders, patient subgroups with better outcomes, and the effect of dose modification on efficacy and safety.

Patients and Methods: Patients were randomized to pazopanib 800 mg/d (n = 557) or sunitinib 50 mg/d, 4 weeks on/2 weeks off (n = 553). Secondary end points included time to complete response (CR)/partial response (PR); the proportion of patients with CR/PR ≥10 months and progression-free survival (PFS) ≥10 months; efficacy in patients with baseline metastasis; and logistic regression analyses of patient characteristics associated with CR/PR ≥10 months. Median PFS, objective response rate (ORR), and safety were evaluated in patients with or without dose reductions or interruptions lasting ≥7 days.

Results: Median time to response was numerically shorter for patients treated with pazopanib versus sunitinib (11.9 vs. 17.4 weeks). Similar percentages of pazopanib and sunitinib patients had CR/PR ≥10 months (14% and 13%, respectively), and PFS ≥10 months (31% and 34%, respectively). For patients without versus with adverse event (AE)-related dose reductions, median PFS, median overall survival, and ORR were 7.3 versus 12.5 months, 21.7 versus 36.8 months, and 22% versus 42% (all $P < .0001$) for pazopanib, and 5.5 versus 13.8 months, 18.1 versus 38.0 months, and 16% versus 34% (all $P < .0001$) for sunitinib; results were similar for dose interruptions.

Conclusion: Dose modifications when required because of AEs were associated with improved efficacy, suggesting that AEs might be used as a surrogate marker of adequate dosing for individual patients.

Keywords

First-line; Sunitinib; Tyrosine kinase inhibitor; VEGF; VEGFR

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Introduction

Pazopanib was approved as first-line treatment for advanced renal cell carcinoma (aRCC) based on the phase III VEG105192 study in which pazopanib significantly prolonged progression-free survival (PFS) compared with placebo (median, 9.2 vs. 4.2 months; $P < .0001$), and this benefit was observed in treatment-naive and cytokine pretreated patients.[1] The randomized phase III COMPARZ study demonstrated noninferior efficacy of first-line pazopanib versus sunitinib.[2] The primary end point of noninferior PFS with pazopanib versus sunitinib was met (8.4 vs. 9.5 months; hazard ratio [HR], 1.05; 95% confidence interval [CI], 0.90-1.22), and the secondary end points of objective response rate (ORR) and overall survival (OS) supported the comparable efficacy of the 2 agents in favorable- and intermediate-risk patient populations. Differences in the safety profile revealed that Grade 3/4 adverse events (AEs) and symptomatic AEs were more frequent with sunitinib compared with pazopanib, and most (11/14) health-related quality of life measures significantly favored pazopanib over sunitinib, a finding that was confirmed in the PISCES patient preference study.[3] Our objectives in this post hoc analysis of COMPARZ were to characterize pazopanib responders and evaluate whether patient subpopulations achieved better outcomes. Furthermore, because of previous observations showing a relationship between pazopanib or sunitinib exposure and efficacy and safety,[4,5] and recent attempts to improve sunitinib's safety profile with alternative sunitinib dosing regimens,[6-9] an additional objective was to evaluate the effect of dose modifications on efficacy and safety outcomes in COMPARZ.

Patients and Methods

Study Design

The COMPARZ study was an international randomized, open-label, noninferiority phase III trial.[2] Briefly, 1110 patients with clear-cell aRCC were randomized 1:1 to receive pazopanib (800 mg once daily; n = 557) or sunitinib (50 mg once daily for 4 weeks, followed by 2 weeks without treatment; n = 553) in 6-week cycles. The primary end point was PFS as assessed by independent review. The study was powered to demonstrate noninferiority of pazopanib versus sunitinib. Secondary end points included OS, safety, and quality of life. COMPARZ was approved by the institutional review board or ethics committee at each participating center and was conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines. Additional post hoc analyses of COMPARZ are reported herein.

Response

Imaging (computed tomography or magnetic resonance imaging) for disease assessment, response, and evaluation according to the Response Evaluation Criteria in Solid Tumors version 1.0 was performed in the intention to treat (ITT) population at baseline, every 6 weeks until week 24, and then every 12 weeks thereafter.[2]

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Safety

Adverse events were recorded and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.[10]

Statistical Analysis

The time to response (complete response [CR]/partial response [PR]) for pazopanib and sunitinib was compared using descriptive statistics. The proportion of patients with a response (CR/PR) or PFS duration ≥10 months in the ITT population was summarized; this is longer than median PFS with pazopanib or sunitinib in the COMPARZ study (8.4 months and 9.5 months, respectively).[2] Median PFS, median OS, and ORR were evaluated for patients with no, any, 1, and ≥ 2 dose reductions or dose interruptions lasting ≥7 days. For PFS and OS, unadjusted HRs and 2-sided log rank *P* values were estimated for patients with no versus any dose reductions or dose interruptions lasting ≥7 days, and for ORR, Fisher's exact test was used to compare patients with no versus any dose reductions or dose interruptions lasting ≥7 days.

The proportion of patients with AEs of special interest (diarrhea, fatigue, hypertension, palmar-plantar erythrodysesthesia [PPE], hematologic AEs, and liver enzyme elevations) in the safety population (patients who received ≥ 1 dose of study drug) were summarized for patients with no, any, 1, or ≥ 2 dose reductions or dose interruptions lasting ≥7 days. The most common (≥5% incidence) AEs leading to dose modifications in either treatment group were evaluated.

Logistic regression analyses were performed in patients with CR/PR duration ≥ 10 months and duration ≥ 18 months, using select demographic and baseline characteristics (Karnofsky Performance Status, number of metastatic sites, number of involved organs, and Memorial Sloan Kettering Cancer Center risk category). No adjustments were made for multiple comparisons. Median PFS, median OS, and ORR were calculated in patients with and without baseline bone, lung, and kidney metastasis from the ITT population.

Results

Efficacy and Response

Of the 171 (30.7%) pazopanib and 137 (24.8%) sunitinib patients who achieved CR/PR (ORR), the median time to response was numerically shorter for pazopanib (11.9 weeks; 95% CI, 11.3-12.1) compared with sunitinib (17.4 weeks; 95% CI, 12.7-18.0; Table 1). A similar percentage of pazopanib and sunitinib patients had a CR/PR response ≥10 months (14% and 13%, respectively) and ≥18 months (6% and 7%, respectively; Table 1). A similar percentage of pazopanib and sunitinib patients also achieved a PFS duration ≥10 months (31% and 34%, respectively) and ≥18 months (14% and 15%, respectively).

Dose Modifications and Efficacy

Dose modifications occurred in similar proportions of patients in the pazopanib and sunitinib groups (see Supplemental Table 1 in the online version). None, any, 1, and ≥2 dose reductions occurred in 56%, 44%, 27%, and 18% of patients with pazopanib and 49%, 51%,

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29%, and 21% of patients with sunitinib. None, any, 1, and ≥2 dose interruptions occurred in 56%, 44%, 25%, and 19% of patients with pazopanib and 51%, 48%, 25%, and 24% of patients with sunitinib. For the pazopanib and sunitinib arms, patients who underwent dose modifications had a lower median average daily dose, with most dose reductions occurring within the first 3 to 6 months of treatment (see Supplemental Figure 1 in the online version). However, median average daily dose increased for patients in the pazopanib group who underwent 1 dose reduction, which might be because of the small number of patients remaining at this later time point (n = 20 at ≥2 years; n = 1 at ≥3 years).

For the pazopanib and sunitinib arms, patients who underwent dose modification had a higher median cumulative dose compared with patients who underwent no dose modification, which is likely explained by the longer time of study treatment for these patients (Table 2). Median PFS for patients with no versus any dose reductions was 7.3 months (95% CI, 5.3-8.3) versus 12.5 months (95% CI, 10.9-15.0; HR, 1.693; 95% CI, 1.365-2.099; $P < .0001$) for pazopanib and 5.5 months (95% CI, 4.3-8.1) versus 13.8 months (95% CI, 11.1-16.4; HR: 1.872; 95% CI, 1.484–2.361; $P < .0001$) for sunitinib (Table 3 and Figure 1). Median OS for patients with no versus any dose reductions was 21.7 months (95% CI, 18.1-24.7) versus 36.8 months (95% CI, 33.1-not estimable [NE]; HR, 2.095; 95% CI, 1.634-2.685; $P < .0001$) for pazopanib and 18.1 months (95% CI, 14.1-23.4) versus 38.0 months (95% CI, 31.5-NE; HR, 2.138; 95% CI, 1.663-2.749; $P < .0001$) for sunitinib (Table 3 and Figure 2). ORR for patients with no versus any dose reductions was 22% (95% CI, 17.1%-26.4%) versus 42% (95% CI, 36.1%-48.4%; difference, 20.5%; 95% CI, 12.8%-28.2%; $P < .0001$) for pazopanib and 16% (95% CI, 11.9%-20.7%) versus 34% (95% CI, 28.0%-39.1%; difference, 17.3%; 95% CI, 10.2%-24.4%; $P < .0001$) for sunitinib (Table 3). Similar findings were observed for patients who underwent dose interruptions of ≥7 days' duration (Table 3 and Figures 1 and 2), suggesting that patients requiring dose modifications because of AEs were more likely to respond and to have a longer PFS and OS.

Predictors of Efficacy and Response

Logistic regression analyses did not identify baseline patient characteristics significantly associated with response in either the pazopanib or sunitinib groups when comparing patients with a CR/PR duration of ≥10 versus <10 months (see Supplemental Table 2 in the online version). Median PFS and median OS in patients with baseline bone, lung, and kidney metastasis were comparable for pazopanib and sunitinib (see Supplemental Table 3 in the online version). ORR was significantly higher for pazopanib versus sunitinib in patients with baseline lung metastasis (36% vs. 28%; $P = .008$).

Safety and Dose Modifications

Select AEs (diarrhea, fatigue, hypertension, PPE, hematologic AEs, and alanine aminotransferase [ALT]/aspartate aminotransferase [AST] elevations) were more frequent in patients who underwent dose reductions or interruptions (see Supplemental Figure 2 in the online version). Consistent with the primary COMPARZ analysis,[2] PPE and hematologic AEs occurred more frequently with sunitinib compared with pazopanib within each dose modification group. For pazopanib and sunitinib, the incidence of AEs was higher with than without dose modification. The most common (≥10%) AEs leading to dose modification

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with pazopanib were hypertension (13%), fatigue (12%), and diarrhea (11%), and the most common AEs leading to dose modification with sunitinib were fatigue (15%), PPE (12%), thrombocytopenia (12%), and diarrhea (10%) (see Supplemental Table 4 in the online version).

Discussion

This post hoc analysis of COMPARZ demonstrated that time to response was excellent with both drugs, although numerically shorter with pazopanib compared with sunitinib; the proportion of patients with a (≥10 months) response was similar for pazopanib (14%) versus sunitinib (13%); and patients who experienced clinical benefit from pazopanib or sunitinib were more likely to have experienced AEs requiring dose modifications.

Time to response for pazopanib in this post hoc analysis is consistent with findings from the trial that led to approval of first-line pazopanib for aRCC, in which the median time to response was also 11.9 weeks according to independent review.[1] With sunitinib, the median time to response in this post hoc analysis was 17.4 weeks, and although this cannot be compared directly with the sunitinib pivotal trial, a pooled analysis of 1059 metastatic renal cell carcinoma (RCC) patients treated with sunitinib across 6 clinical trials (including the pivotal trial) found a median time to response of 10.6 weeks.[11] The patient population in the pooled clinical trial analysis was treatment-naive or cytokine pretreated, treated with sunitinib 50 mg/d (4/2 schedule) or continuous sunitinib 37.5 mg/d,[11] and were thus a more heterogeneous patient population than in COMPARZ.

In this post hoc analysis of the COMPARZ trial, pazopanib and sunitinib were associated with a similar proportion of patients who had a response duration ≥10 months, as well as associated with comparable median PFS and median OS in patients with baseline bone, lung, and kidney metastasis. The noninferior efficacy and differentiated safety profile of first-line pazopanib and sunitinib treatment is supported by large real-world analyses.[12-14]

Patients who underwent dose modifications because of AEs continued therapy for longer periods of time, had significantly improved PFS, OS, and ORR, received a higher median cumulative dose, and ultimately had more toxicity reported compared with patients who underwent no dose modifications. Within each dose modification group, select AEs (PPE and hematologic AEs) were more common with sunitinib compared with pazopanib and liver enzyme elevations were more common with pazopanib, consistent with the primary analysis.[2] This highlights the need for better therapy management for these patients, which might include dose reduction and treatment interruptions, which could ultimately lead to improved clinical outcomes.

Although other analyses of clinical studies support that increased exposure to pazopanib and sunitinib is associated with improved clinical outcomes, the current post hoc analysis of COMPARZ extends this by suggesting that dose modifications when required because of toxicity do not compromise efficacy. Further, this analysis suggests that patients who do undergo dose reductions because of AEs continue treatment longer and are more likely to experience clinical benefit from pazopanib and sunitinib compared with patients who

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experience minimal toxicity. Thus, dose reductions and dose interruptions are safe for patients who experience toxicity from pazopanib or sunitinib. A retrospective analysis of 2 prospective sunitinib trials similarly demonstrated improved median PFS and ORR in patients who underwent dose reduction because of AEs compared with patients who remained on the standard 50 mg/d, 4/2 schedule.[15] A real-world study of 591 metastatic RCC patients treated with first-line pazopanib or sunitinib in Italy also suggested that dose modifications when necessary for AEs do not compromise efficacy.[16] In contrast, a chart review of 10 oncology centers in Europe (n = 291) found significantly shorter survival for aRCC patients who received a low relative dose intensity (RDI) of pazopanib or sunitinib (RDI <0.7),[17] as might be expected based on pharmacokinetic data demonstrating a positive relationship between pazopanib/sunitinib exposure and survival.[4,5] However, 19% of patients in the European chart review had initiated treatment at a lower than standard dose, and thus lower doses received in this patient population were not all due to toxicity.[17] Finally, a recent study in the adjuvant setting showed that higher pazopanib levels were associated with improved disease-free survival and did not increase treatment discontinuations or Grade 3/4 AEs, with the exception of hypertension.[18] This highlights the important role of drug exposure on clinical outcomes; dose modifications should only be considered for patients who require this intervention because of AEs.

The relationship between exposure and efficacy end points has been demonstrated for several approved vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKIs), including pazopanib and sunitinib.[4,5,19] Higher sunitinib exposure has been shown to be associated with longer time to progression and greater OS in a pooled clinical trial analysis of metastatic RCC patients.[4] Similarly, survival benefits have been shown for pazopanib. In a large phase II trial of pazopanib in /metastatic RCC patients, a steady-state trough concentration of 20.5 μg/mL was identified as the cutoff associated with improved PFS and tumor shrinkage, and a relationship between increased pazopanib exposure and the frequency of AEs, such as hypertension and liver enzyme elevations, was shown.[5] Indeed, high interpatient variability in drug exposure is observed with VEGFR TKIs, such as pazopanib and sunitinib,[20,21] and patients achieving higher drug exposure are also more likely to experience toxicity as well as survival benefit. This higher toxicity might lead to dose reductions or interruptions, which might explain the superior clinical outcomes (PFS, OS, and ORR) in patients with dose modifications compared with patients without dose modifications.

With sunitinib, the safety profile at the approved dose of 50 mg/d for 4 weeks followed by 2 weeks off treatment (4/2 schedule) has led to investigation of alternative off-label dose schedules, such as the 2/1 schedule[6,7] and continuous 37.5 mg/d dosing (Renal EFFECT trial).[8] Although the Renal EFFECT study did not lead to a change in practice, the 2:1 schedule for patients experiencing toxicity with the 4:2 schedule has been widely used. Outcomes from a single-arm phase II trial of individualized sunitinib dosing also support dose/schedule individualization in patients experiencing AEs.[9] In this individualized-dosing study, dose reductions and schedule changes were implemented in patients experiencing grade ≥2 toxicity, and patients experiencing minimal toxicity received dose escalation (18.4%). The median PFS was 12.5 months and median OS was 38.5 months. The ORR (46.1%) and stable disease rate (38.5%) translated into a clinical benefit for 84.6% of

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patients with no decline in quality of life scores during therapy. Although multiple studies have assessed the effect of nonstandard intermittent dosing schedules with sunitinib to maintain therapeutic drug concentrations, prolong duration of therapy, minimize AEs, and/or maintain efficacy, we are unaware of any clinical studies prospectively investigating intermittent pazopanib dosing schedules in patients with aRCC. However, a recent preclinical study reported that a high-dose intermittent pazopanib dosing schedule was able to extend median OS in an animal model of advanced metastatic RCC resistant to continuous pazopanib,[22] suggesting potential clinical utility for intermittent pazopanib dose scheduling for selected patients with aRCC.

The association between tolerability and clinical outcomes underscores that clinical outcomes are not adversely affected in patients with treatment-related AEs who undergo dose reductions and remain on therapy. This supports individual dosing titrated according to toxicity. Although patients without toxicity have worse outcomes, the consequences of this on dosing and treatment strategy are less clear. Dose reductions should only be applied following presentation of treatment-related AEs dose reductions are not an intervention that improves long-term outcomes, but rather a necessity to keep patients on treatment. Whether patients who experience minimal toxicity should be dose escalated is a valid question that should be addressed by future studies. Initial observations suggest TKI dose escalation during treatment may be appropriate for selected patients with metastatic RCC. In a retrospective analysis of 25 patients whose disease progressed during sunitinib treatment, 36% had a PRand 28% had stable disease for a median of 7.5 months after dose escalation.[23] In the phase II study of individualized sunitinib treatment previously discussed, 18.4% of patients were dose escalated.[9] Axitinib titration was associated with improved response rates in a randomized phase II trial.[24] In a retrospective analysis of 22 patients who received an escalated TKI dose (axitinib [17], sunitinib [3], pazopanib [2]) after progressive disease, 4 (22%) patients experienced a PR and 78% had a decreased disease burden after dose escalation.[25] Individualizing axitinib dose and treatment duration based on toxicity with planned breaks of therapy has been reported to be feasible and active.[26]

Limitations of this study are the post hoc, retrospective nature of the analyses. Furthermore, no adjustments were made for multiple comparisons, limiting the conclusions that can be drawn from the efficacy by baseline metastatic site data.

In summary, these results suggest that clinicians treating aRCC patients with sunitinib or pazopanib should reduce the dosage and/or give treatment breaks if required because of AEs, which might allow patients to remain longer on treatment and continue to obtain clinical benefit. Differences revealed between first-line pazopanib and sunitinib may also aid treatment choice for clinicians, such as the shorter time to response and lower frequency of PPE and hematologic AEs with pazopanib, and lower frequency of ALT/AST elevations with sunitinib.

Conclusion

In this post hoc analysis of the COMPARZ study, patients who required dose reductions and dose interruptions due to AEs experienced longer time on treatment, received greater

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cumulative doses, and had significantly improved PFS, OS, and ORR compared with patients who did not require dose modifications. This indicates that dose modifications can be safely implemented without compromising pazopanib or sunitinib efficacy, and that AEs might be used as a surrogate marker of adequate dosing for individual patients.

Clinical Practice Points

- In the phase III COMPARZ study, first-line pazopanib was noninferior to first-line sunitinib with regard to efficacy in metastatic RCC; safety and quality of life profiles favored pazopanib.
- In this post hoc analysis of COMPARZ, a similar percentage of patients with pazopanib and sunitinib had a response duration (CR/PR or PFS) ≥10 months.
- The median time to response was 11.9 weeks with pazopanib versus 17.4 weeks with sunitinib.
- Within both arms, patients with AE-related dose modifications had higher cumulative doses; longer time on treatment, significantly improved PFS, OS, and ORR; and more frequent AEs versus patients with no dose modification.
- These findings suggest that clinicians can safely alter pazopanib or sunitinib dosing because of AEs without compromising efficacy and that AEs might be used as a surrogate marker of adequate dosing for each patient.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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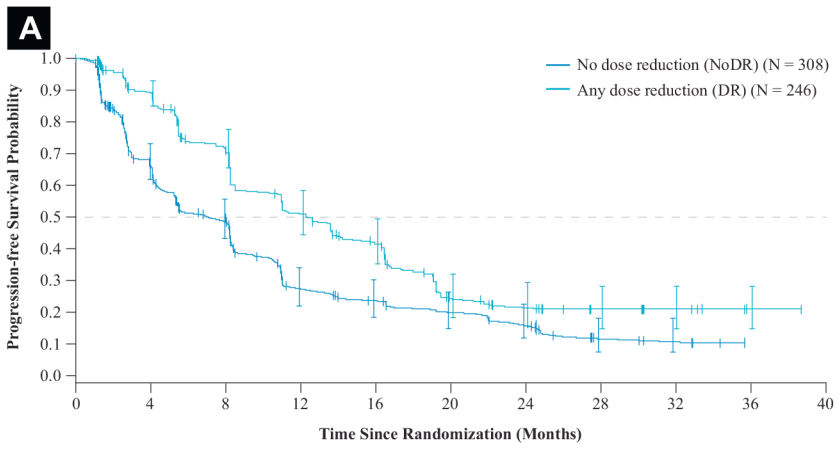
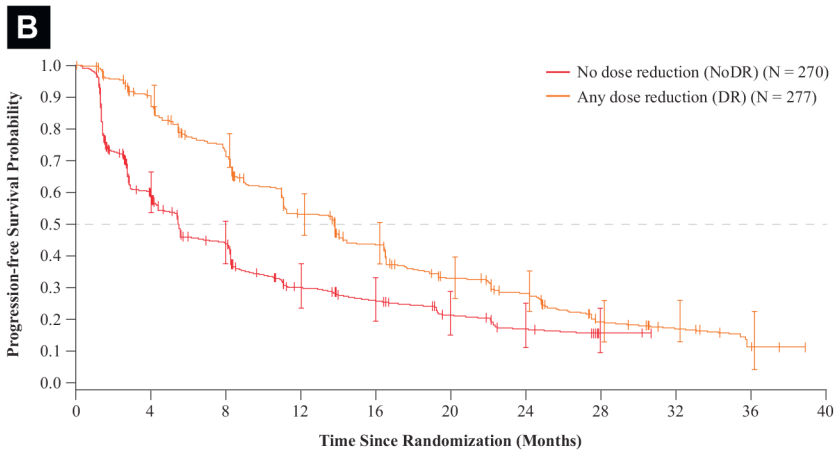


Number of patients at risk for pazopanib:

NoDR	308	166	107	48	38	30	24	9	7	0	0
DR	246	195	138	88	67	31	22	10	6	1	0



Number of patients at risk for sunitinib:

NoDR	270	118	74	39	29	18	11	2	0	0	0
DR	277	233	175	108	82	51	37	16	10	3	0

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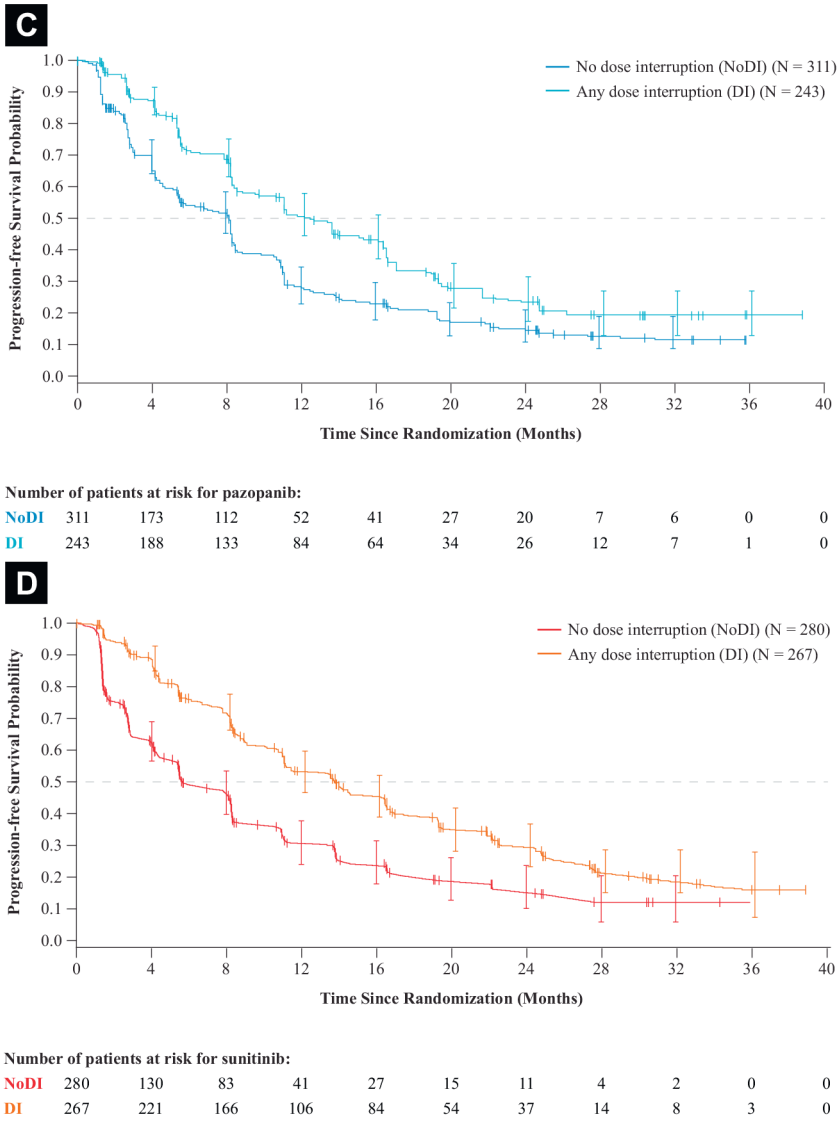

Figure 1.

Kaplane–Meier Plots of Progression-Free Survival in Patients With and Without Dose Reductions With Pazopanib (A) and Sunitinib (B), and in Patients With and Without Dose Interruptions With Pazopanib (C) and Sunitinib (D). Error Bars Indicate 95% CIs

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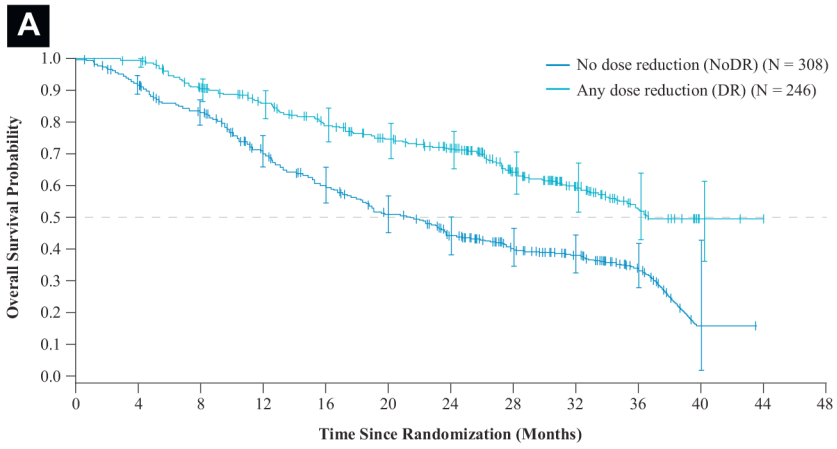
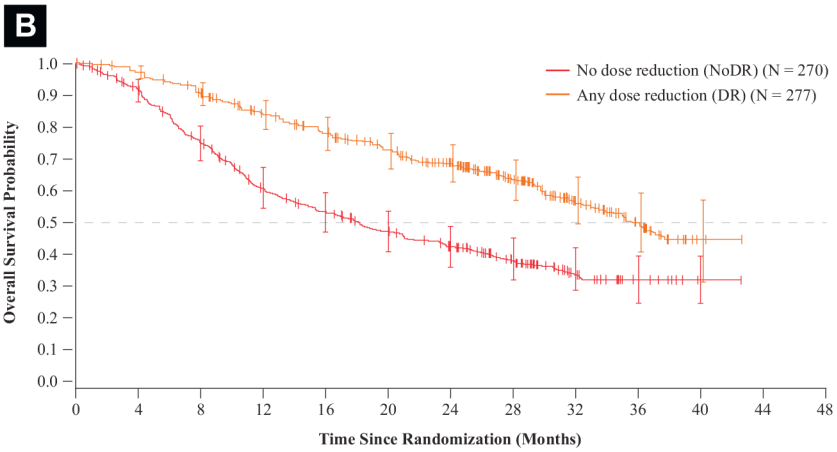


Number of patients at risk for pazopanib:

NoDR	308	277	245	195	161	132	103	71	45	14	1	0	0
DR	246	244	213	189	166	142	120	71	37	14	2	0	0



Number of patients at risk for sunitinib:

NoDR	270	232	185	142	121	102	85	57	24	8	1	0	0
DR	277	269	246	212	192	167	140	91	45	20	2	0	0

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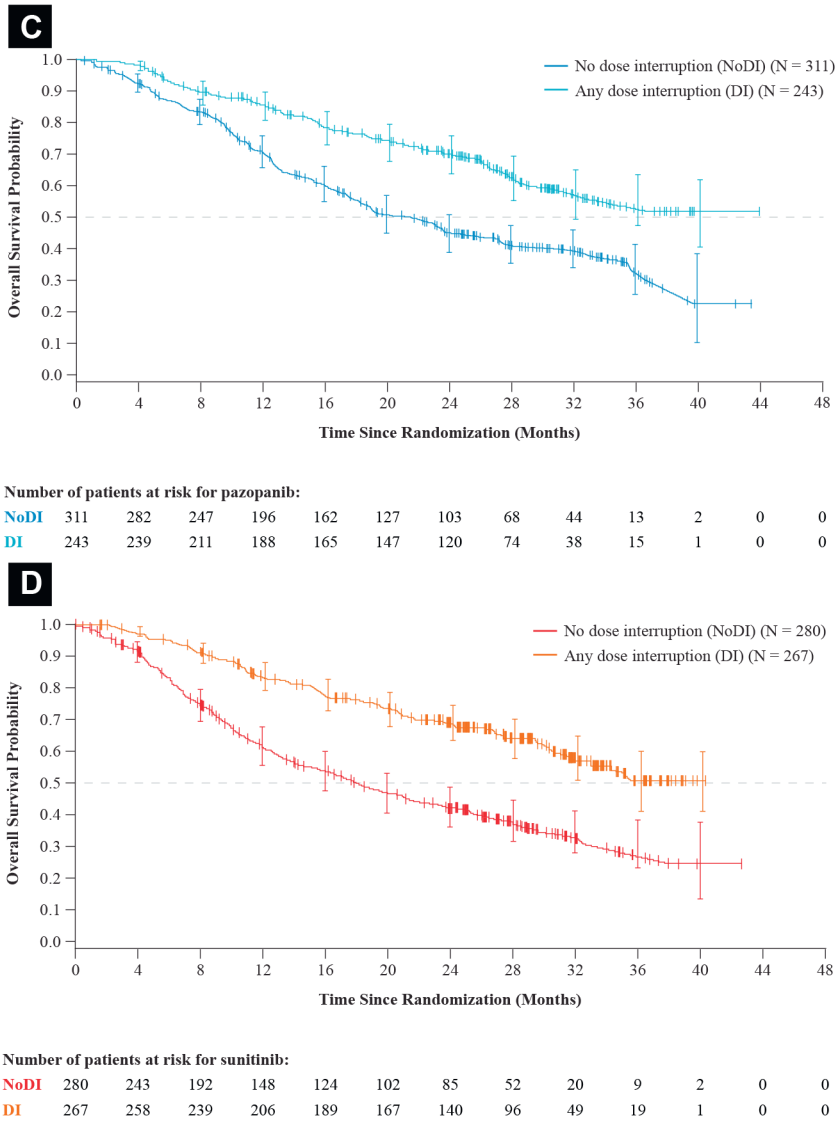

Figure 2.

Kaplane–Meier Plots of Overall Survival in Patients With and Without Dose Reductions With Pazopanib (A) and Sunitinib (B), and in Patients With and Without Dose Interruptions With Pazopanib (C) and Sunitinib (D). Error Bars Indicate 95% CIs

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Table 1

Time to Response (CR/PR) and Proportion of Patients Who Achieved CR/PR or PFS ≥10 Months and ≥18 Months (ITT Population)

	Pazopanib (n = 557)	**Sunitinib (n = 553)**
Patients Who Achieved CR/PR, n[a]	171	137
Time to Response (CR/PR), Weeks[b]		
First quartile (95% CI)	6.0 (6.0-6.3)	11.6 (8.3-12.0)
Median (95% CI)	11.9 (11.3-12.1)	17.4 (12.7-18.0)
Third quartile (95% CI)	17.6 (12.9-18.1)	30.1 (23.1-35.9)
CR/PR Duration		
≥10 Months, n/n (%)	76/557 (14)	74/553 (13)
Progressed or died, n/n (%)	38/76 (50)	33/74 (45)
Censored, follow-up ended, n/n (%)	13/76 (17)	20/74 (27)
Censored, follow-up ongoing, n/n (%)	25/76 (33)	21/74 (28)
≥18 Months, n/n (%)	34/557 (6)	38/553 (7)
Progressed or died, n/n (%)	8/34 (24)	13/38 (34)
Censored, follow-up ended, n/n (%)	6/34 (18)	10/38 (26)
Censored, follow-up ongoing, n/n (%)	20/34 (59)	15/38 (39)
PFS Duration, n (%)		
≥10 Months	175 (31)	186 (34)
≥18 Months	79 (14)	**85 (15)**

Abbreviations: CI = confidence interval; CR = complete response; ITT = intention to treat; PFS = progression-free survival; PR = partial response.

[a]The time to response analysis was restricted to the subgroup of patients who experienced a CR/PR.

[b]Time to response is defined as the time from the start of treatment until the first documented evidence of confirmed CR or PR, whichever comes first.

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Table 2

Median Time on Treatment and Cumulative Dose (Safety Population)

	Median Cumulative Dose, ×1000 mg (Range)		Median Time of Study Treatment, Months (Range)	
	Pazopanib (n = 554)	**Sunitinib (n = 548)**	**Pazopanib (n = 554)**	**Sunitinib (n = 548)**
Dose Reduction(s)				
None	134.4 (1.6-940.0)	4.2 (0.05-39.15)	5.6 (0-39)	3.7 (0-38)
Any	165.2 (9.6-804.0)	8.825 (0.80-32.25)	10.1 (1-40)	10.8 (1-38)
1	169.4 (9.6-804.0)	8.013 (0.80-29.05)	8.9 (1-40)	9.2 (1-38)
≥2	150.2 (21.2-750.2)	10.406 (1.713-32.25)	11.4 (1-39)	13.7 (2-37)
Dose Interruption(s) ≥7 Days				
None	116.8 (1.6-887.2)	2.85 (0.50-32.20)	5.1 (0-40)	2.3 (0-37)
Any	116.0 (15.2-940.0)	9.294 (0.80-39.15)	9.6 (1-39)	10.6 (1-38)
1	108.0 (15.2-940.0)	5.95 (0.80-29.55)	6.7 (1-39)	6.5 (1-29)
≥2	218.6 (21.6-804.0)	11.25 (1.588-39.15)	13.9 (2-39)	14 (2-38)

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Table 3

PFS, OS, and ORR in the ITT Population by Dose Modification Group

	Median PFS, Months (95% CI)		Median OS, Months (95% CI)		ORR, n (%) [95% CI][a]	
	Pazopanib (n = 554)	**Sunitinib (n = 548)**	**Pazopanib (n = 554)**	**Sunitinib (n = 548)**	**Pazopanib (n = 554)**	**Sunitinib (n = 548)**
Dose Reduction(s)						
None	7.3 (5.3-8.3)	5.5 (4.3-8.1)	21.7 (18.1-24.7)	18.1 (14.1-23.4)	67 (22) [17.1-26.4]	44 (16) [11.9-20.7]
Any	12.5 (10.9-15.0)	13.8 (11.1-16.4)	36.8 (33.1-NE)	38.0 (31.5-NE)	104 (42) [36.1-48.4]	93 (34) [28.0-39.1]
None versus any	HR, 1.693 (95% CI, 1.365-2.099); $P < .0001$	HR, 1.872 (95% CI, 1.484-2.361); $P < .0001$	HR, 2.095 (95% CI, 1.634-2.685); $P < .0001$	HR, 2.138 (95% CI, 1.663-2.749); $P < .0001$	Difference: 20.5% (95% CI, 12.8%-28.2%); $P < .0001$	Difference: 17.3% (95% CI, 10.2%-24.4%); $P < .0001$
1	11.1 (8.3-13.5)	11.1 (10.2-13.8)	33.1 (27.2-NE)	30.3 (24.7-NE)	49 (33) [25.7-41.0]	50 (31) [23.9-38.2]
≥2	16.4 (11.1-18.6)	16.5 (11.5-19.3)	NR (NE-NE)	NR (34.9-NE)	55 (56) [45.8-65.3]	43 (37) [28.3-45.9]
Dose Interruption(s) ≥7 Days						
None	8.2 (5.5-8.3)	5.6 (5.4-8.2)	21.7 (17.8-26.0)	18.1 (14.2-23.2)	72 (23) [18.5-27.8]	46 (16) [12.1-20.8]
Any	12.6 (9.9-16.4)	13.8 (11.1-16.6)	NR (31.6-NE)	NR (32.1-NE)	99 (41) [34.6-46.9]	91 (34) [28.4-39.8]
None versus any	HR: 1.648 (95% CI, 1.329-2.043); $P < .0001$	HR: 1.923 (95% CI, 1.529-2.418); $P < .0001$	HR: 1.959 (95% CI, 1.528-2.511); $P < .0001$	HR: 2.264 (95% CI, 1.762-2.909); $P < .0001$	Difference: 17.6% (95% CI, 9.8%-25.3%); $P < .0001$	Difference: 17.7% (95% CI, 10.5%-24.8%); $P < .0001$
1	8.3 (6.0-11.0)	11.0 (8.2-14.0)	31.6 (26.5-NE)	30.5 (23.7-NE)	42 (30) [22.8-38.1]	40 (30) [21.9-37.3]
≥2	16.7 (13.7-19.4)	16.6 (13.6-19.6)	NR (36.8-NE)	NR (34.9-NE)	57 (54) [44.8-63.8]	51 (39) [30.3-46.9]

Abbreviations: CI = confidence interval; HR = hazard ratio; ITT = intention to treat; NE = not estimable; NR = not reached; OS = overall survival; ORR = objective response rate; PFS = progression-free survival.

[a]Percentage was calculated using the number of patients in the corresponding dose modification group (see Supplemental Table 1 in the online version) as the denominator.

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