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## Adjuvant Pazopanib Versus Placebo After Nephrectomy in Patients With Localized or Locally Advanced Renal Cell Carcinoma: Final Overall Survival Analysis of the Phase 3 PROTECT Trial

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## Abstract

Most studies indicate no benefit of adjuvant therapy with VEGFR tyrosine kinase inhibitors in advanced renal cell carcinoma (RCC). PROTECT (NCT01235962) was a randomized, double-blind, placebo-controlled phase 3 study to evaluate adjuvant pazopanib in patients with locally advanced RCC at high risk of relapse after nephrectomy (pazopanib,  $n = 769$ ; placebo,  $n = 769$ ). The results of the primary analysis showed no difference in disease-free survival between pazopanib 600 mg and placebo. Here we report the final overall survival (OS) analysis (median follow-up: pazopanib, 76 mo, interquartile range [IQR] 66–84; placebo, 77 mo, IQR 69–85). There was no significant difference in OS between the pazopanib and placebo arms (hazard ratio 1.0, 95% confidence interval 0.80–1.26; nominal  $p > 0.9$ ). OS was worse for patients with T4 disease compared to those with less advanced disease and was better for patients with body mass index (BMI)  $\geq 30$  kg/m<sup>2</sup> compared to those with lower BMI. OS was significantly better for patients who remained disease-free at 2 yr after treatment compared with those who relapsed within 2 yr. These findings are consistent with the primary outcomes from PROTECT, indicating that adjuvant pazopanib does not confer a benefit in terms of OS for patients following resection of locally advanced RCC.

## Patient summary:

In the randomized, double-blind, placebo-controlled phase 3 PROTECT study, overall survival was similar for patients with locally advanced renal cell carcinoma (RCC) at high risk of relapse after nephrectomy who received adjuvant therapy with pazopanib or placebo. Pazopanib is not recommended as adjuvant therapy following resection of locally advanced RCC.

## Keywords

Pazopanib; Renal cell carcinoma; Tyrosine kinase inhibitor

VEGFR tyrosine kinase inhibitors are successfully used in the treatment of advanced renal cell carcinoma (RCC). However, most studies indicate no benefit of these agents in terms of overall survival (OS) in the adjuvant setting. Of the five studies reported (ASSURE [1,2], SORCE [3], ATLAS [4], S-TRAC [5], and PROTECT [6]), only S-TRAC reported a significant improvement in disease-free survival (DFS) associated with adjuvant sunitinib [5]. PROTECT (NCT01235962) was a randomized, double-blind, placebo-controlled phase 3 study to evaluate adjuvant pazopanib in patients with locally advanced RCC at high risk of relapse after nephrectomy [6]. The results of the primary analysis (data cutoff October 15, 2015) showed no difference in DFS between pazopanib 600 mg and placebo (hazard ratio [HR] 0.86, 95% confidence interval [CI] 0.70–1.1;  $p = 0.17$ ). Higher pazopanib trough plasma concentrations ( $C_{\text{trough}}$ ) levels were associated with better DFS but did not increase treatment discontinuations or grade 3/4 adverse events (AEs), with the exception of hypertension [7]. In this report, we present the final overall survival (OS) analysis from the PROTECT trial (data cutoff April 15, 2019).

The design and primary outcomes from PROTECT have been reported previously [6]. Patients with nonmetastatic RCC and predominant clear-cell histology at high risk of recurrence (advanced T stage, nodal positive status, and high tumor grade) were randomly assigned to receive pazopanib or placebo for 1 yr. A pazopanib starting dose of 800 mg/d was initially administered (pazopanib,  $n = 198$ ; placebo,  $n = 205$ ), but this was reduced to 600 mg/d following a blinded safety review that indicated a higher than expected discontinuation rate with the higher dose. The protocol was approved by institutional review boards and independent ethics committees, and all patients provided written informed consent.

The primary endpoint was DFS in the intent-to-treat pazopanib 600 mg (ITT<sub>600 mg</sub>) population; OS was evaluated as a secondary endpoint. Survival was assessed every 6 mo until death, study completion, or study termination. In this analysis, OS is summarized for the overall intent-to-treat population (ITT<sub>ALL</sub>) using the Kaplan-Meier method and compared between treatment arms using a stratified log-rank test (stratification factors were pathologically determined TNM stage and Fuhrman grades). Multivariable Cox regression analysis was used to assess the impact of baseline characteristics on OS. Multivariable analyses were exploratory and were not prespecified in the protocol.

A total of 1538 patients were enrolled (pazopanib,  $n = 769$ ; placebo,  $n = 769$ ). At April 15, 2019, all patients had completed the study or withdrawn (Supplementary Fig. 1). As previously reported, patient characteristics were well balanced between the treatment arms and the primary analysis showed no difference in DFS between placebo and pazopanib (data cutoff October 15, 2016; Supplementary Table 1 and Supplementary Table 2) [6].

Analysis of OS for a median follow-up duration of 76 mo (interquartile range [IQR] 66–84) in the pazopanib arm and 77 mo (IQR 69–85) in the placebo arm for patients without a death

event showed no significant difference between the treatment arms (ITT<sub>ALL</sub>: HR 1.0, 95% CI 0.80–1.26; nominal  $p > 0.9$ ; Fig. 1A). Deaths were reported for 145 participants in the pazopanib arm and 150 in the placebo arm, and median OS was not estimable because of the small number of events. OS was worse for patients with T4 disease compared to those with less advanced T stage (T1/2 and T3), and was better for patients with body mass index (BMI)  $\geq 30$  kg/m<sup>2</sup> compared with those with lower BMI (Fig. 1B,C). OS was better for patients who remained disease-free at 2 yr after treatment compared with those who relapsed within 2 yr (Fig. 1D). OS according to BMI and T stage in each treatment arm is shown in Supplementary Figure 2 and Supplementary Figure 3. Among patients receiving pazopanib, there was no difference in OS between those with high and low  $C_{\text{trough}}$  levels ( $>25$  or  $\leq 20.5$   $\mu\text{g/ml}$ ) at weeks 3–5 or weeks 16–20 (Supplementary Fig. 4). There was also no difference in OS between the pazopanib and placebo arms for the subgroup of patients in the ITT<sub>800</sub> population who were randomly assigned before the reduction in pazopanib starting dose to 600 mg/d (Supplementary Fig. 5).

On multivariable analysis, T4 disease, high Fuhrman grade, stage T3 disease, and Latin America location were associated with a higher risk of death, and BMI  $\geq 30$  kg/m<sup>2</sup> was associated with a lower risk of death (Table 1).

The most frequent subsequent systemic treatments were VEGFR or mTOR inhibitors (pazopanib, 25% [191/769]; placebo, 26% [201/769]). Sixty-five (8.5%) of the patients receiving pazopanib and 56 (7.3%) of those receiving placebo received a subsequent immunotherapy regimen.

Since the cutoff date for the primary analysis, nine additional AEs have been reported in six patients receiving pazopanib 600 mg and 11 AEs in ten patients receiving placebo; none were considered treatment-related. Serious AEs included cardiac failure in the pazopanib arm, and Kaposi's sarcoma, thrombocytopenia, breast cancer, and cerebrovascular accident in the placebo arm.

In summary, these analyses indicate that adjuvant pazopanib confers no OS benefit for patients with localized or locally advanced RCC following nephrectomy. AE reporting was consistent with the known safety profile of pazopanib in advanced RCC. These findings are also consistent with the updated analysis of the ASSURE study, which failed to show a significant difference in OS between adjuvant sunitinib or sorafenib and placebo in patients with clear cell RCC [2].

Multivariable Cox model analyses from our study suggest that patients with BMI  $\geq 30$  kg/m<sup>2</sup> have a 41% lower risk of death compared with those with BMI  $< 25$  kg/m<sup>2</sup>. This observation supports the “obesity paradox”, whereby overweight or obese patients are at higher risk of clear cell RCC but, conversely, also have better prognosis than normal-weight patients with RCC [8,9]. It has been suggested that although BMI is not an independent predictor of mortality, tumors that develop in obese patients with RCC may be more indolent, possibly related to differences in the expression of genes involved in metabolic and fatty acid pathways, such as fatty acid synthase [8]. Although they are unlikely to inform clinical decision-making, these data suggest that body weight should be considered

as a stratification factor in future clinical trials. The present data also indicate that the risk of death was less than three times higher for patients with T4 disease and 42% higher for those with T3 disease compared to patients with T1/2 disease. Landmark analysis using the Kaplan-Meier method showed that patients remaining disease free at 2 yr after randomization had significantly better OS than those with disease recurrence within 2 yr. This finding highlights the poor outcome—median OS of 63.8 mo—for patients who have relapses relatively early, within 2 yr of nephrectomy.

In conclusion, these findings add to the primary outcomes from the PROTECT study, which indicated that adjuvant pazopanib 600 mg does not prolong DFS following resection of locally advanced RCC. Survival analysis showed no difference in OS between the treatment arms. Pazopanib is not recommended as adjuvant therapy following resection of locally advanced RCC.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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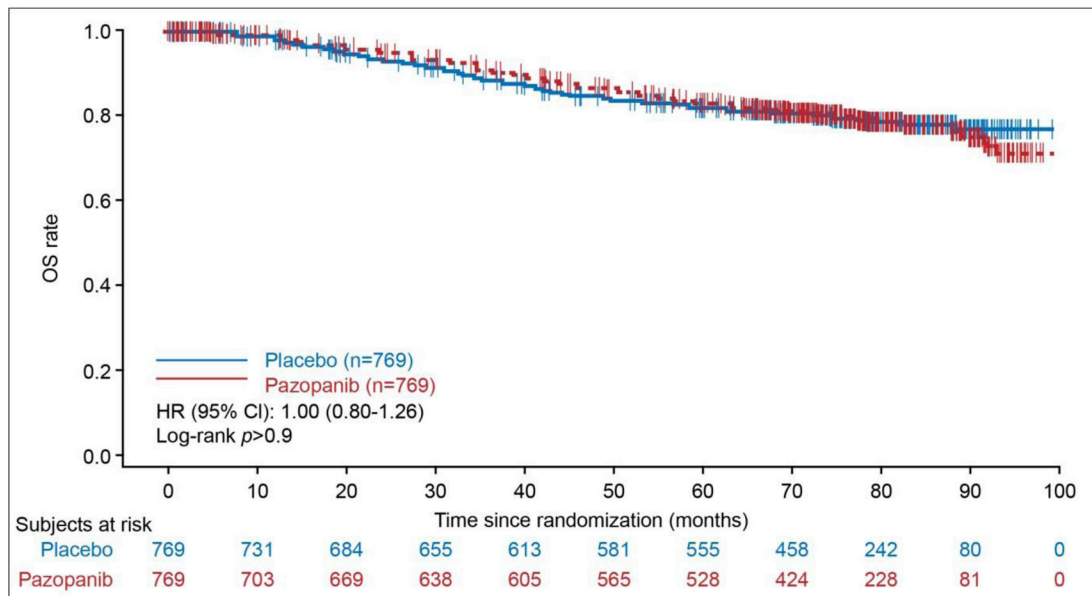
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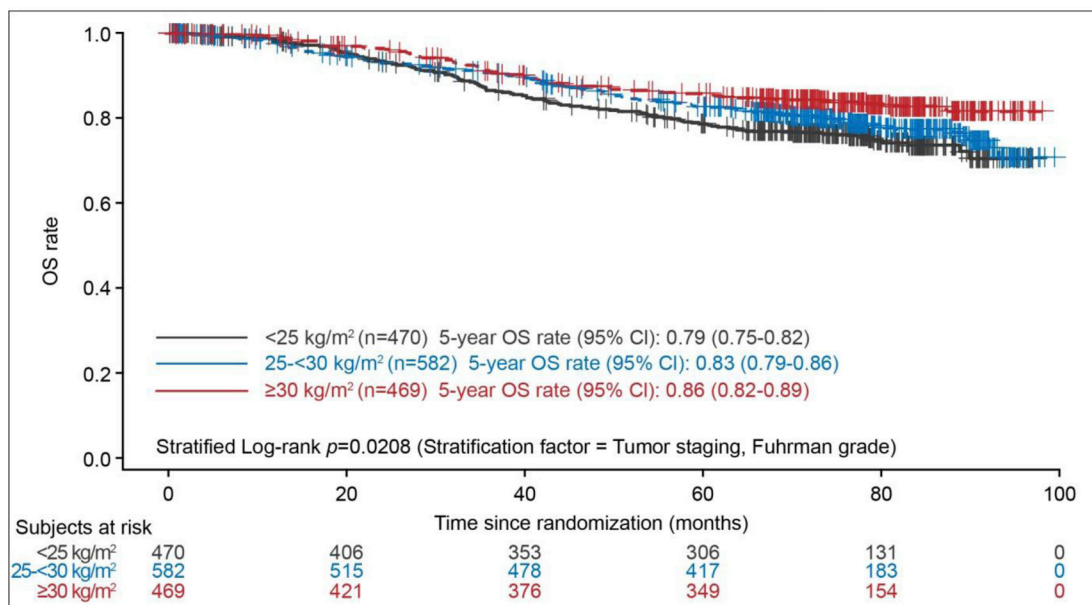
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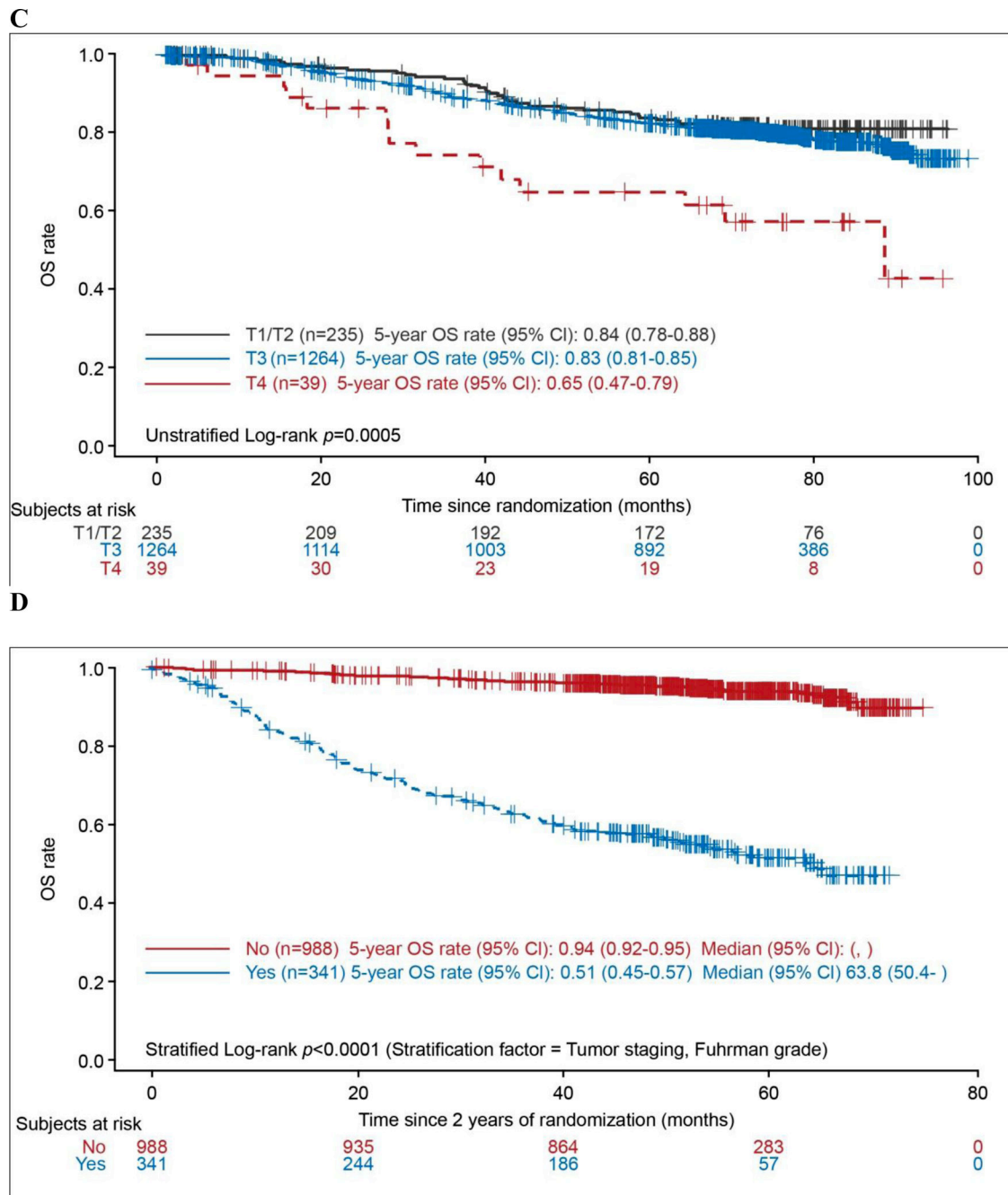
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A



B





**Fig. 1 –.** Overall survival in the pooled intent-to-treat group (all patients from the ITT pazopanib 600 mg, and ITT pazopanib 800 mg populations) according to (A) treatment arm, (B) body mass index, (C) T stage, and (D) disease relapse within 2 yr (landmark analysis). BMI = body mass index; CI = confidence interval; DFS = disease-free survival; HR = hazard ratio; OS = overall survival; ITT = intent to treat.



**Table 1 –**Multivariable Cox model<sup>a</sup> of analysis of overall survival

	Pazopanib (n = 769)	Placebo (n = 769)	Multivariable Cox model	
			HR	p value
BMI, n (%)				
<25 kg/m <sup>2</sup>	234 (30.4)	236 (31)	Reference	
25 to <30 kg/m <sup>2</sup>	281 (37)	301 (39)	0.802	0.11
30 kg/m <sup>2</sup>	246 (32)	223 (29)	<b>0.592</b>	<b>0.001</b>
T stage, n (%)				
T1/T2	117 (15)	118 (15)	Reference	
T3	634 (82)	630 (82)	<b>1.417</b>	<b>0.050</b>
T4	18 (2.3)	21 (2.7)	<b>3.312</b>	<b>&lt;0.001</b>
Fuhrman grade, n (%) <sup>b</sup>				
High (grade 3/4)	534 (69)	485 (63)	<b>1.641</b>	<b>&lt;0.001</b>
Low (grade 1/2)	235 (31)	282 (37)	Reference	
Region, n (%)				
Asia Pacific	86 (11)	86 (11)	0.745	0.2
Europe	432 (56)	447 (58)	1.243	0.14
Latin America	44 (5.7)	34 (4.4)	<b>1.784</b>	<b>0.025</b>
North America	207 (27)	202 (26)	Reference	

BMI = body mass index; HR = hazard ratio.

<sup>a</sup>Sex, BMI, T stage, Fuhrman grade, region, race (Asian vs non-Asian)<sup>c</sup>, and treatment were entered in a Cox model to build a final model to best fit the data using a forward selection algorithm with entry criterion of  $p < 0.05$ . The final Cox model includes treatment group (forced to the model), BMI group, T stage, Fuhrman grade, and region. Interaction effects of BMI and sex on overall survival were not significant and were therefore not included in the final model. Overall survival is defined as the time from randomization until death due to any cause. The length of this interval is calculated as the date of death minus the date of randomization plus 1 d. For subjects who do not die, time to death will be censored at the last date of known contact (as recorded in the electronic case report form).

<sup>b</sup>Two patients in the placebo arm had missing Fuhrman grade.

<sup>c</sup>Twenty-nine patients (pazopanib  $n = 19$ ; placebo  $n = 10$ ) had missing race data.

Variables that are significantly associated with OS are indicated using bold font.