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A Phase I/II study to assess the safety and efficacy of pazopanib and pembrolizumab combination therapy in patients with advanced renal cell carcinoma

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Author contribution statement

SC, JRI, RP, PA, and DFM conceived and designed the study. RP and DFM conducted the literature search. MHV, TA, PA, IN, and AR collected and assembled the data. MHV, RP, TA, PA, IN, AR, and DFM analyzed and interpreted the data. SC, JRI, and DFM supervised the study. All authors participated in the interpretation of the data and writing and review of the manuscript.

Declaration of interests

MHV reports grants from BMS; personal fees from Corvus, Exelixis, and Eisai; and grants and personal fees from Pfizer, outside the submitted work. DFMcD reports grants from BMS, Pfizer, Merck, Alkemes, Genetech, Exelixis, and X4 Pharma and personal fees from BMS, EMP Sereno, Eli Lilly Company, Merck, Pfizer, and Alkemes, outside the submitted work. TA reports personal fee from Bayer, Biontech, Beigene, Servier, Roche, outside the submitted work. MV reports personal fees from MSD, AstraZeneca, and BMS, outside the submitted work. PA and IN are employees of Novartis Pharma AG, Basel, Switzerland. AR is an employee of Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA.

Data sharing statement

Novartis is committed to sharing the access to patient-level data and supporting clinical documents from eligible studies with qualified external researchers. These requests are reviewed and approved by an independent review panel based on scientific merit. All data provided are anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations.

This trial data availability is according to the criteria and process described on www.clinicalstudydatarequest.com.

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Abstract

Background: This study assessed whether antiangiogenic treatment may potentiate immune checkpoint blockade in patients with advanced renal cell carcinoma (RCC).

Materials and Methods: This was an open-label, two-part, multicenter study involving treatment-naïve patients with advanced RCC. Part 1 consisted of a Phase I dose-escalation and expansion of pazopanib plus pembrolizumab (combination therapy). Cohorts A and B received pazopanib in combination with pembrolizumab, whereas Cohort C received pazopanib monotherapy for 9 weeks before receiving the combination therapy. Part 2 was planned as a randomized three-arm study but was not conducted.

Results: Overall, 42 patients were enrolled (10 each in Cohorts A and B, 22 in Cohort C). The MTD was not reached and the RP2D was not declared as Cohort C was closed early because of safety concerns. The ORRs were 60% and 20% in Cohorts A and B, respectively. In Cohort C, the ORRs were 33%, 25%, and 0% in the combination therapy, pembrolizumab monotherapy, and pazopanib monotherapy groups, respectively. The median PFS was 21.95 months and 41.40 months in Cohorts A and B, respectively. Grade 3/4 AEs were observed in 90% of patients in Cohorts A and B. In Cohort C, the frequencies of Grade 3/4 AEs, SAEs, and AEs leading to dose reduction were typically high in the combination therapy group.

Conclusion: Despite preliminary signs of efficacy, significant hepatotoxicity was observed in Cohorts A and B. The sequential schedule of pazopanib followed by pazopanib plus pembrolizumab showed reduced hepatotoxicity; however, other safety issues emerged with this approach.

Micro-abstract

This open-label, two-part, multicenter study involving 42 treatment-naïve patients with advanced RCC assessed the possibility of an immune checkpoint blockade in combination with antiangiogenic treatment. The overall clinical benefit rate of 60% showed encouraging efficacy across cohorts. However, significant safety issues associated with this treatment indicated that this combination is unsafe.

Keywords

VEGF-TKI; TKI/IO; immune checkpoint inhibitor; antiangiogenic; immuno-oncology

INTRODUCTION

Renal cell carcinoma (RCC) is the most common type of kidney cancer, and advanced RCC or metastatic RCC (mRCC) is almost always a fatal disease.[1] The prognosis for patients with advanced RCC or mRCC is poor, with a 5-year survival rate of less than 10%.[2]

Overexpression of vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor α (PDGFR-α) has been identified in a majority of patients with RCC.[3–6] Over the past decade, treatment with tyrosine kinase inhibitors (TKIs) targeting

antiangiogenic pathways has been the standard of care for patients with mRCC. However, the disease invariably becomes resistant to TKI therapy,[7, 8] warranting more durable responses. Beyond its proangiogenic role in RCC tumor biology, preclinical studies have implicated the VEGF pathway in tumor immune evasion.[9] Accordingly, a rationale exists for combining VEGF-directed therapy with immune checkpoint inhibitors based on this cross-talk between the VEGF pathway, tumor microenvironment, and tumor-infiltrating lymphocytes.[9] VEGF inhibition may modulate the host tumor microenvironment and reduce immune tumor suppression via several mechanisms, whereas the checkpoint inhibitors activate the host's antitumor immune response by blocking negative regulatory immune signals.[10, 11]

Durable responses have been reported with several different checkpoint inhibitors across a broad range of human cancers, substantiating the hypothesis that cancer immunotherapy through checkpoint inhibitors is active in a range of indications.[12–15] Proof-of-concept studies of immune checkpoint inhibitors have shown activity in mRCC. Nivolumab, a fully human immunoglobulin G4 (IgG4) anti– programmed death 1 (PD-1) antibody, demonstrated objective responses (~20%) and a manageable safety profile in patients with mRCC.[14, 16] In a large Phase II cohort study of patients with mRCC, pembrolizumab, an anti–PD-1 antibody, demonstrated promising efficacy and acceptable tolerability.[17, 18] Atezolizumab, an anti–programmed death ligand 1 (PD-L1) antibody, demonstrated durable antitumor effects in patients with mRCC.[19] The preliminary results on immune checkpoint inhibitors led to a series of clinical trials that resulted in regulatory approval of nivolumab and the combination of ipilimumab plus nivolumab for the treatment of advanced RCC.

Treatment of mRCC with checkpoint inhibitors in combination with targeted agents is expected to achieve improved clinical outcomes compared with monotherapy.[20] Several trials have evaluated checkpoint inhibitors in combination with targeted agents in patients with mRCC, increasing the options in frontline mRCC therapy. At the time this study began in September 2013, no data had been generated for targeted agents in combination with checkpoint inhibitors in RCC.

This open-label, two-part, multicenter study of pazopanib in combination with pembrolizumab was the first planned exploration designed to assess whether antiangiogenic treatment with pazopanib may potentiate immunotherapy with pembrolizumab in patients with treatment-naïve advanced RCC. Pazopanib, an oral angiogenesis inhibitor targeting VEGFR-1, −2, and −3; PDGFR-α and -β; and the stem cell factor receptor c-KIT, is indicated for the treatment of advanced RCC and advanced soft tissue sarcoma.[21, 22] Pembrolizumab, a humanized IgG4 monoclonal antibody, binds with a high affinity to PD-1, inhibiting its interaction with PD-L1 and PD-L2. Although pembrolizumab is indicated for the treatment of various solid tumors and Hodgkin's lymphoma, it was not yet indicated for RCC treatment at the onset of this study. The results of this study were previously disclosed as an oral presentation at the 2017 American Society of Clinical Oncology (ASCO) Annual Meeting.[23]

MATERIALS and METHODS

Patients

Eligible patients were aged 18 years or above; had locally advanced RCC or mRCC with predominantly clear-cell histology and no prior systemic therapy; had at least one measurable lesion as evaluated according to the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1[24]; had an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0 or 1 (on a scale from 0 to 5, with lower scores indicating lower disability)[25]; had adequate organ function; and had a left ventricular ejection fraction ≥ the lower limit of normal (determined using echocardiography or multiple-gated acquisition). The study was approved by the independent ethics committee or institutional review board for each center, and informed consent was obtained from each patient before performing study-specific procedures or assessments.

Objectives

The primary objective of the study was to determine the safety, tolerability, maximum tolerated dose (MTD), and recommended Phase II dose (RP2D) of pazopanib in combination with pembrolizumab in treatment-naïve patients with advanced RCC. Secondary objectives included determining the pharmacokinetics (PK) and clinical activity of this combination therapy.

Study design and treatments

This was an open-label, two-part, multicenter study of pazopanib and/or pembrolizumab in treatment-naïve patients with advanced RCC and mRCC.

Part 1 consisted of a Phase I dose-escalation study of pazopanib plus pembrolizumab (combination therapy), followed by an expansion study to determine the MTD and RP2D. Part 2 was a randomized three-arm study to evaluate the clinical efficacy and safety of pazopanib plus pembrolizumab compared with single-agent pazopanib and single-agent pembrolizumab. Part 2 of the study was not conducted.

Part 1: dose escalation

A modified 3+3 design was followed for dose escalation. The patients included in a cohort were assigned to one dose level for the duration of the study. Dose modifications were allowed based on the observed toxicities.

In Part 1, at least three patients were planned to receive the combination therapy (pazopanib + pembrolizumab). Starting doses were 800 mg orally once daily (QD; continuous dosing) for pazopanib and 2 mg/kg intravenously (IV) every 2 weeks (Q2W) for pembrolizumab. The maximum combination dose level was 800 mg QD (continuous dosing) pazopanib and 10 mg/kg IV (Q2W) pembrolizumab.

Patients were evaluated for a minimum of 8 weeks before the next dose level cohort was enrolled. MTD was defined as the highest dose of pazopanib in combination with the highest dose of pembrolizumab at which no more than one of six patients experienced dose-limiting

toxicities (DLTs) after a minimum of 8 weeks of treatment. If two or more patients in a six-patient cohort experienced a DLT, the MTD was considered as exceeded.

DLT was defined as a drug-related adverse event (AE) starting in the first 8 weeks of treatment and meeting one of the following criteria: febrile neutropenia; Grade 4 thrombocytopenia; Grade 4 nonhematological toxicity; Grade 3 clinically significant nonhematological drug-related toxicities that could not be managed with adequate supportive therapy within 14 days of the onset of the event; aspartate aminotransferase (AST)/alanine aminotransferase (ALT) >3.0 × the upper limit of normal (ULN) with concomitant elevation in bilirubin; and any ≥Grade 2 eye pain or reduction in visual acuity that did not respond to topical therapy and did not improve to Grade 1 severity within 2 weeks of the initiation of topical therapy or required systemic treatment or a ≥Grade 3 toxicity occurring beyond the first 8 weeks of treatment.

Patients who withdrew from the study before the completion of 8 weeks of treatment for reasons other than DLT could be replaced. Of the six patients enrolled, five were evaluable and one had a DLT.

Overall, 20 patients were enrolled in the dose-expansion Cohorts A and B of Part 1 before Cohort C was added.

- Cohort A (patients treated with the combination therapy [n=10]; six from the dose-escalation period and four newly enrolled): pazopanib (800 mg QD) plus pembrolizumab (2 mg/kg every 3 weeks [Q3W])
- Cohort B (patients treated with the combination therapy [n=10]): pazopanib (600 mg QD) plus pembrolizumab (2 mg/kg Q3W)

The frequency of the infusion was implemented Q3W based on emerging data from the use of pembrolizumab as a single agent.

To mitigate the toxicity observed in Cohorts A and B, hence a dose expansion Cohort C was started to assess if the introduction of a 9-week safety run-in period with pazopanib would improve tolerability. Cohort C included a run-in period of 9 weeks with single-agent pazopanib to select patients who would tolerate pazopanib as a single agent before starting the combination. Following the 9-week safety run-in, patients were assessed based on laboratory and safety parameters to confirm eligibility to receive the combination therapy. Part 2 of the study was closed before enrolling patients, and the Part 1 treatment regimen for Cohort C was modified to allow continuation on single-agent pembrolizumab or pazopanib following the run-in period.

Biomarkers

Blood and tumor tissue samples were collected during the study. The date and time of biopsy for these tissue samples (fresh or archived) were recorded. Furthermore, to characterize the biomarkers related to the activity of pazopanib and pembrolizumab in this patient population, tissue biomarkers were assessed in baseline tissues (original diagnosis or a recent biopsy), tissues obtained at the end of the run-in period (Part 1, Cohort C), and tissues obtained at disease progression.

Analysis of blood biomarkers included whole blood and plasma cytokines and angiogenic factors. Whole blood peripheral blood mononuclear cells and cDNA were collected, but not analyzed. These samples may be analyzed at a later date.

Data analysis and statistical considerations

No formal statistical hypotheses were tested. Only descriptive methods were used in the analysis of the data obtained. Efficacy and safety analyses were based on all patients who received at least one dose of pazopanib or pembrolizumab (all-treated population). Analysis of the PK for pazopanib and pembrolizumab was based on all patients in the all-treated population who provided at least one evaluable PK concentration for pazopanib and pembrolizumab, respectively.

Role of the funding source

This study was sponsored by Novartis, in collaboration with Merck & Co. The responsibility for site monitoring resided with the GSK (until March 2015) and Novartis (after March 2015) field monitors. Final analyses and writing of the report were performed by Novartis and confirmed by Merck & Co. All authors had full access to the data and contributed to the development and approval of the manuscript. The corresponding author had full access to the data throughout the study and had final responsibility for the decision to submit for publication.

RESULTS

A total of 42 patients were enrolled from three centers in the United States (US) and two centers in the United Kingdom (UK). One patient did not receive any treatment because of ascites on Day 1 and was not clinically suitable for treatment.

Demographics

In all three cohorts, demographic characteristics were similar except for age (median age: 61, 57, and 61 years in Cohorts A, B, and C, respectively) and sex (50%, 70%, and 71% of patients were men in Cohorts A, B, and C, respectively; Table 1). 5 patients had liver metastasis at baseline.

In the Cohort C post–run-in period, the demographic characteristics were similar in all three treatment groups.

Dose escalation

In this period, six patients were enrolled and treated with pazopanib 800 mg QD plus pembrolizumab 2 mg/kg IV Q2W. All patients were then included in Cohort A in the dose-expansion period.

Dose-expansion period

In Cohort A, 10 patients were enrolled (six patients from the dose-escalation period and four newly enrolled) and were treated with pazopanib 800 mg QD plus pembrolizumab 2 mg/kg IV Q3W. In Cohort B, 10 new patients were enrolled, and all patients received

treatment with pazopanib 600 mg QD plus pembrolizumab 2 mg/kg IV Q3W. In Cohort C, 22 new patients were enrolled, and 21 patients were treated (run-in period only or run-in and post–run-in periods). One patient did not receive any treatment because of ascites on Day 1 and was not clinically suitable for treatment. Patient dispositions in the different periods are presented in Figure 1.

Of the 22 patients enrolled in the dose-expansion Cohort C, only 12 patients continued receiving treatment after the run-in period. At the end of the run-in period, based on the strict safety criteria, only six patients were eligible to pursue the combination therapy (pazopanib at the final dose of the run-in and pembrolizumab 2 mg/kg Q3W), four received pembrolizumab monotherapy at 2 mg/kg Q3W, and two received pazopanib monotherapy at the final dose of run-in. Although the hepatotoxicity observed in Cohorts A and B was limited, with the safety run-in introduced in Cohort C, additional AEs emerged, leading to dose reductions (40%) and interruptions (80%). In addition, three out of six patients treated with the combination therapy in Cohort C experienced DLTs (Grade 3 pneumonitis, Grade 3 bowel perforation, and Grade 4 lipase increased). Therefore, despite encouraging signs of clinical activity, the potential harm from the treatment was found to outweigh the potential benefits. Consequently, the sponsor, in agreement with the steering committee, decided to stop enrollment for Part 1, and the initiation of the combination therapy in patients already in the run-in period (Cohort C) was also stopped. Part 2 of the study was not initiated, and the Part 1 treatment regimen for Cohort C was modified to allow continuation on single-agent pembrolizumab or pazopanib following the run-in period.

Maximum tolerated dose and recommended Phase II dose

The MTD was not reached and the RP2D was not declared as the last cohort (Cohort C) was closed to further recruitment because of safety concerns.

Safety

Overview of adverse events: All patients experienced at least one AE related to the study treatment in all the cohorts. In Cohorts A and B, 90% of patients each had at least one Grade 3/4 AE. In Cohort C, the frequencies of Grade 3/4 AEs, serious adverse events (SAEs), and AEs leading to dose reduction were typically higher in the combination therapy treatment group versus the two monotherapy treatment groups (Table 2). During the run-in period, the most commonly reported AEs (>50% of patients) were diarrhea (57%) and nausea (52%).

Dose-limiting toxicities: DLTs were reported in two patients in Cohort A, five patients in Cohort B, and four patients in Cohort C. Cohort A: Grade 3 ALT increased (two patients; 20%), Grade 3 AST increased (two patients; 20%), and Grade 3 blood bilirubin increased (one patient; 10%); Cohort B: Grade 4 ALT increased (one patient; 10%), Grade 3 AST increased (three patients; 30%), Grade 3 ALT increased (one patient; 10%), and Grade 1 and Grade 3 lipase increased (one patient each; 10%); Cohort C: DLTs were reported in one patient during the run-in period (treatment with pazopanib monotherapy) and in three patients during the post–run-in period (treatment with the combination therapy).

Run-in period (patients treated with pazopanib monotherapy): Grade 3 ALT increased (one patient); post– run-in period (patients treated with the combination therapy): Grade 3 large intestine perforation (one patient), Grade 4 lipase increased (one patient), and Grade 2 and Grade 3 pneumonitis (one patient each).

A summary of AEs for Cohorts A, B, and C is presented in Table 3. All patients had at least one AE. The most commonly reported AEs for Cohorts A and B were ALT increased (70% in each cohort) and AST increased (70% in Cohort A and 80% in Cohort B). During the post–run-in period, the most frequent AEs were diarrhea and hypertension (five patients each) in the combination therapy treatment group; diarrhea, ALT increased, and AST increased (four patients each) in the pembrolizumab monotherapy treatment group; and nausea (eight patients), diarrhea, fatigue, and vomiting (seven patients each) in the pazopanib monotherapy treatment group. During the run-in period, the most commonly reported AEs (>50% of patients) were diarrhea (12 patients; 57%) and nausea (11 patients; 52%). Diarrhea was also the most commonly reported AE during the post–run-in period (7/12 patients; 58.3%; Table 3). A summary of AEs by maximum Grade 3–5 for Cohorts A, B, and C is presented in Table 4.

Adverse events suspected to be study drug related

Pazopanib: The incidences of AEs related to pazopanib were similar in Cohorts A and B. ALT increased, AST increased, diarrhea (in Cohorts A and B), nausea (in Cohort A only), and hypertension (in Cohort B only) were the only AEs observed in more than 50% of patients. In the Cohort C post–run-in period, the most frequent AEs related to pazopanib were diarrhea, nausea, and hypertension in the combination therapy treatment group; ALT increased and AST increased in the pembrolizumab monotherapy treatment group; and nausea, diarrhea, and vomiting in the pazopanib monotherapy treatment group (Table 5).

Pembrolizumab: In Cohorts A and B, the most commonly reported (in ≥50% of patients in both cohorts) AEs suspected to be related to pembrolizumab were AST increased and ALT increased. In the Cohort C post–run-in period, diarrhea was the most commonly reported AE related to pembrolizumab for both treatment groups (33% of patients in the combination therapy treatment group and 50% of patients in the pembrolizumab monotherapy treatment group; Table 6).

Deaths and other serious or clinically significant adverse events

Deaths: A total of two patients died; one patient from Cohort B died while on treatment (death was not suspected to be related to the study treatment, neither with pembrolizumab nor with pazopanib) and the other from Cohort C died of an unknown cause during follow-up, 7 months after the last dose of pazopanib in the combination therapy.

Serious adverse events

Serious adverse events suspected to be related to pazopanib: In Cohorts A and B, the most commonly reported SAE related to pazopanib was ALT increased (30% of patients in Cohort A and 40% of patients in Cohort B). In Cohort B, AST increased (three patients; 30%) was also frequently reported as an SAE, suspected to be related to pazopanib.

In Cohort C, liver function test increased, diarrhea, large intestine perforation, dehydration, hepatic function abnormal, and pneumonitis (one patient each) were reported as SAEs related to pazopanib.

Serious adverse events suspected to be related to pembrolizumab: In Cohorts A and B, ALT increased and AST increased were the most common SAEs suspected to be related to pembrolizumab. The proportion of patients having these drug-related SAEs was lower in Cohort A (ALT increased: 20% of patients; AST increased: 10% of patients) than in Cohort B (ALT increased: 40% of patients; AST increased: 20% of patients).

In Cohort C, diarrhea, large intestine perforation, and pneumonitis (one patient each) were the SAEs suspected to be related to pembrolizumab.

Extent of exposure

Pazopanib: Pazopanib exposure was similar in Cohort A and Cohort B, with numerical differences that could be attributed to the small number of patients (n=10) in each cohort. Overall, 90% and 70% of patients in Cohorts A and B, respectively, were treated for less than 18 months (Table 7).

In the Cohort C run-in and post–run-in periods, patients in the combination therapy treatment group received pazopanib for a longer duration (median exposure: 11.4 months) compared with those in the monotherapy treatment groups (pembrolizumab, median exposure: 1.9 months; pazopanib, median exposure: 1.9 months). None of the patients in either of the monotherapy treatment groups received pazopanib for 6 months or more.

Dose reduction/dose interruptions of pazopanib: Overall, seven (70%), six (60%), and nine (43%) patients had pazopanib dose reductions and seven (70%), seven (70%), and 11 (52%) patients had pazopanib dose interruptions in Cohorts A, B, and C, respectively. The primary reason for pazopanib dose reductions was AEs in 78%, 71%, and 92% of patients and the primary reason for pazopanib dose interruptions was AEs in 57%, 70%, and 88% of patients in Cohorts A, B, and C, respectively. Most pazopanib dose interruptions lasted for less than 7 days (~60%, and in most cases, patients were able to restart treatment).

Adverse events leading to dose adjustment and/or dose interruption: The most commonly reported AEs requiring dose adjustment or interruption were ALT increased and AST increased (five patients in each of the three cohorts). In general, AEs were resolved after the dose was decreased or temporarily interrupted or after the event was treated with appropriate interventionThe dose used of systemic steroids to treat AEs ranged from 4mg to 100mg. The AEs requiring treatment with glucocorticoids include pneumonitis (n=3), transaminitis (n=1), diarrhea (n=2), rash (n=3) LFTs and increased lipase (n=1 each).

Pembrolizumab: Compared with Cohort B, the mean and median times on pembrolizumab monotherapy were higher in Cohort A; however, in both cohorts, 50% of patients received treatment for 18 months or more.

In the Cohort C post–run-in period, exposure to pembrolizumab was similar in the combination therapy group versus the pembrolizumab monotherapy group. Most patients in each treatment group were treated for less than 18 months.

Dose interruptions of pembrolizumab: Most patients had pembrolizumab dose delays in Cohort A (90% of patients) and Cohort B (80% of patients). Dose delays of pembrolizumab were less frequent in patients in Cohort C (24% of patients). No dose interruption of pembrolizumab occurred in Cohorts A and B. One patient had a pembrolizumab dose interruption in Cohort C.

Efficacy results

Best response: The overall response rates (ORRs; complete response [CR] or partial response [PR]) were 60% (6/10 patients, two CRs and four PRs) and 20% (2/10 patients, one CR and one PR) in Cohorts A and B, respectively. Two patients (20%) in Cohort A and one patient (10%) in Cohort B had CR. Progressive disease (PD) was reported in one patient in Cohort B. Stable disease (SD) was observed in four patients (40%) in Cohort A and in seven patients (70%) in Cohort B. The clinical benefit rate (CBR) was the same for both cohorts (60%).

In Cohort C, the ORRs (CR or PR) were 33%, 25%, and 0% in patients from the combination therapy, pembrolizumab monotherapy, and pazopanib monotherapy treatment groups, respectively. CR was reported in one patient (25%) treated with pembrolizumab monotherapy. PD was reported in one patient each from the combination therapy and pembrolizumab monotherapy groups. SD was observed in three patients (50%) treated with the combination therapy, two patients (50%) treated with pembrolizumab, and six patients (55%) treated with pazopanib monotherapy (Table 8).

In the pazopanib monotherapy treatment group, 45% of the patients were not evaluable (best overall response could not be derived in these patients because only one evaluation was available, and no confirmation response could be derived) and the other 55% had SD.

Progression-free survival: The 18-month progression-free survival (PFS) rates were 56% and 88% in Cohorts A and B, respectively. The median PFS (95% confidence interval [CI]) was 21.95 (7.62, not applicable) months in Cohort A and 41.40 (2.76, 41.69) months in Cohort B. Similar findings were observed in the efficacy endpoints when the modified RECIST criteria were used.

In the Cohort C post–run-in period, the 18-month PFS rate was 20% in patients treated with the combination therapy and 50% in patients treated with pembrolizumab monotherapy. No events occurred at or before 18 months in the group treated with pazopanib monotherapy.

The median PFS (95% CI) was 15.90 (4.90, 26.05) months in patients treated with the combination therapy and 13.16 (1.58, not applicable) months in patients treated with pembrolizumab monotherapy. Similar findings were observed for the efficacy endpoints when the modified RECIST criteria were used.

Pharmacokinetics: At steady state, pazopanib C_{trough} concentrations were similar between the pazopanib monotherapy and combination therapy groups in the Cohort C run-in and post–run-in periods. Pazopanib concentrations as shown by C_{max} increased with an increase in dose from 600 to 800 mg. In Cohort B, the geometric mean C_{trough} plasma pazopanib concentrations at Weeks 9 and 10 were 17.4 μg/mL and 32.7 μg/mL, respectively. The geometric mean trough plasma pazopanib concentration at Week 4 was 28.1 μg/mL in the Cohort C run-in period. The geometric mean trough plasma pazopanib concentration was 32.1 μg/mL at Week 10 in the Cohort C post–run-in period.

In Cohort A, pembrolizumab steady-state concentrations were generally attained after Cycle 7, and the geometric mean C_{trough} concentrations were between 42.5 μg/mL and 53.5 μg/mL at steady state. The coefficient of variation of the geometric mean trough concentrations of pembrolizumab in Cohort A was between 13.4% and 46.7% beyond Cycle 7 at steady state.

In Cohort B, pembrolizumab steady-state concentrations were generally attained after Cycle 13, and the geometric mean C_{trough} concentrations were between 37.2 μg/mL and 42.4 μg/mL at steady state. The coefficient of variation of the geometric mean trough concentrations of pembrolizumab in Cohort B was between 6.1% and 11.9% beyond Cycle 13 at steady state.

In the Cohort C post–run-in period, pembrolizumab steady-state concentrations were attained after Cycle 7, and the geometric mean C_{trough} concentrations were between 23.6 μg/mL and 35.1 μg/mL at steady state. The coefficient of variation of the geometric mean trough concentrations of pembrolizumab in Cohort C was between 26.9% and 44.7% at steady state.

Exploratory biomarkers: The expression of immune cell proteins in tissue (monitored using immunohistochemistry) and in circulating whole blood (monitored using flow cytometry) was not constant across patients in the three cohorts. The mean tumor-relative mRNA levels at baseline were similar among the three cohorts for the immune cell–related genes *APOE*, *CD163*, *CD209*, *CD68*, *CD8A*, *CD8B*, *CHIT1*, *CSF1R*, *CXCL5*, *FLT3LG*, *FOXP3*, *GNLY*, *GZMA*, *GZMH*, *MARCO*, *MSR1*, *PDCD1*, and *PRF1*. There were no apparent differences across cohorts and no large patient-to-patient variability for all immune cell biomarkers tested.

DISCUSSION

Single-agent therapy with immune checkpoint inhibitors has demonstrated clinical benefit in patients with mRCC.[26] Studies have shown a role for VEGF in immune evasion as well as tumor angiogenesis in several tumor types.[9] Moreover, in mRCC, VEGF has been reported to increase the levels of regulatory T cells, thereby maintaining immunosuppression.[27] Combination of immune checkpoint inhibitors and VEGF inhibitors is a proposed hypothesis for the interplay between the immune system and angiogenesis in RCC. Preclinical studies have tested the combination of VEGF signaling blockade and immune checkpoint inhibition, and have demonstrated synergistic effects of this combination.[9] Pazopanib is a standard of care treatment for mRCC.[22] Immunomodulatory

effects of pazopanib have been demonstrated through in vitro and in vivo studies, providing a strong rationale for the use of pazopanib in combination with immune checkpoint inhibitors.[9] The efficacy of single-agent pembrolizumab has been demonstrated recently in KEYNOTE-427.[28] The current Phase II study was designed to assess the safety and efficacy of pazopanib plus pembrolizumab in mRCC.

The combination showed encouraging efficacy with an overall CBR of 60%. Nevertheless, significant hepatotoxicity, with the most frequent (≥30%) SAEs being ALT and AST elevations, made this combination unsafe to take forward. Notably, hepatotoxicity reduction through sequential administration of pazopanib followed by the combination therapy (pazopanib + pembrolizumab) was successful. However, other safety issues emerged in patients treated with this approach.

TKI-immune checkpoint inhibitor combinations have demonstrated superior efficacy with manageable toxicity in selected pivotal studies, leading to the approval of such combinations. Combined treatment with pembrolizumab plus axitinib in treatment-naïve patients with previously advanced RCC resulted in a significantly longer overall survival (OS) and PFS and a significantly higher objective response rate than with sunitinib, with a similar overall toxicity in the two groups.[29] A longer PFS was observed with avelumab plus axitinib versus sunitinib alone in patients with previously untreated advanced RCC.[30] This study led to the approval of the avelumab plus axitinib combination for treating patients with treatment-naïve advanced RCC. A randomized Phase III trial of atezolizumab combined with bevacizumab showed a longer PFS compared with sunitinib in previously untreated PD-L1 positive patients with mRCC; however, no OS benefit was observed with this combination.[31] Nivolumab and cabozantinib showed superior efficacy in terms of PFS, OS, and response rate, and the benefit was consistent compared with sunitinib in numerous subgroups, which led to the approval of this combination as a first-line therapy for RCC.[32]

The clinical activity of VEGF-targeted therapies in combination with PD-L1/PD-1 blockade has been demonstrated in different studies,[26, 33, 34] but these combinations showed substantial toxicities in a majority of the studies, thereby limiting their use[34] even though some of these combinations, such as axitinib plus avelumab[30] and axitinib plus pembrolizumab, were successful in demonstrating superior efficacy.[29, 35] Selection of suitable TKI appears to play an important role in tolerability of TKI and immune checkpoint inhibitor combinations.[36]

Unlike other TKIs used in RCC, pazopanib has a black box warning for causing severe and fatal hepatotoxicity.[21] Fatal hepatic failure was reported in 0.2% of patients in the pivotal trial; many of the Grade 3/4 toxicities noted with pazopanib in patients with RCC were hepatic in nature, with elevations of AST, ALT, and bilirubin levels.[22] A meta-analysis of pazopanib trials showed the occurrence of transaminase elevations in most patients treated with pazopanib at 3–9 weeks after therapy initiation, which resolved with a median time of 30 days following onset. In addition, it was noted that the rechallenge after resolution of the event was successful without liver failure. However, close monitoring of liver chemistry was recommended by the authors.[37] Furthermore, in a real-world study, which retrospectively assessed the incidence of pazopanib-induced liver toxicity in patients with mRCC in the UK,

the authors noticed lower hepatotoxicity rates (30%) compared with that in clinical trials, with most cases being mild and requiring no treatment modifications; age, PS, or presence of liver metastases did not show any association with hepatotoxicity.[38] Pazopanib-induced active hepatitis[39] and lethal hepatotoxicity[40] have been recently described in case reports. In a patient who was treated with nivolumab in the third-line setting followed by fourth-line pazopanib, the authors hypothesized that lethal hepatotoxicity induced by pazopanib was because of the enhanced immunological reactions that were initially induced by nivolumab; the use of immunosuppressive treatment, such as glucocorticoids, is recommended in cases of severe hepatotoxicity due to treatment with a TKI followed by an immune checkpoint inhibitor.[40] Thus far, the mechanism of pazopanib-induced hepatotoxicity remains unclear, although several preclinical and clinical studies have attempted to understand the possible mechanism.[41–43]

The CheckMate-016 study, which was in part designed to assess the combination of nivolumab with sunitinib or pazopanib in mRCC, also reported substantial toxicity with greater frequencies of high-grade treatment-related AEs and AEs leading to discontinuation than those previously observed with nivolumab, sunitinib, or pazopanib monotherapy.[34] Although sustained antitumor activity was observed with the nivolumab and pazopanib combination (ORR 45%), DLTs including abnormal liver function led to the discontinuation of the study.[44] It appears that the tolerability of such combinations is highly dependent on the choice of TKI, with a possible synergistic or additive toxicity effect.[36]

Several factors might have been associated with the outcomes in patients treated with these combinations, and there is a significant need to identify the prognostic factors associated with these outcomes. Biomarker analysis in the IMmotion 150 study demonstrated that relative expression of angiogenesis T-effector/interferon-γ response and myeloid inflammatory gene expression signatures were strongly and differentially associated with PFS within and across treatments. Therefore, further understanding of these molecular profiles might offer mechanistic insights into how angiogenesis blockage could overcome the resistance to the immune checkpoint blockade.[45]

CONCLUSION

Despite preliminary signs of efficacy, the harm from the combination of pazopanib and pembrolizumab appeared to outweigh the potential benefits in patients with treatment-naive advanced or metastatic RCC. Hence, further clinical development of the combination will not be pursued in this population. This pazopanib plus pembrolizumab trial highlights the importance of well-conducted clinical research and is a cautionary note about the application of PD-1 blockade–based combination therapy. It shows that differences in the choice of TKI influence the tolerability when combined with immune checkpoint inhibitor therapy. TKI/checkpoint inhibitor combinations remain a potential option for many patients with mRCC; however, there is a need to balance both safety and efficacy in future algorithms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CBR	clinical benefit rate
CI	confidence interval
CR	complete response
DLT	dose-limiting toxicity
ECOG PS	Eastern Cooperative Oncology Group performance status
IgG	immunoglobulin G
IV	intravenous
mRCC	metastatic renal cell carcinoma
MTD	maximum tolerated dose
ORR	overall response rate
OS	overall survival
PD	progressive disease
PD-1	programmed death 1
PDGFR	platelet-derived growth factor receptor
PD-L1	programmed death ligand 1
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response

Q2W	every 2 weeks
Q3W	every 3 weeks
QD	once daily
RCC	renal cell carcinoma
RP2D	recommended Phase II dose
SAE	serious adverse event
SD	stable disease
TKI	tyrosine kinase inhibitor
UK	United Kingdom
US	United States
VEGFR	vascular endothelial growth factor receptor

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Highlights

- This study was the first to assess combination of pazopanib with pembrolizumab in patients with aRCC.
- The combination showed an encouraging efficacy, with an overall CBR of 60%.
- However, significant hepatotoxicity made this combination unsafe to pursue further.
- This trial is a cautionary note about the application of PD-1 blockade–based combination therapy.
- Differences in TKI might influence the tolerability when combined with CPI immune therapy.

CLINICAL PRACTICE POINTS

- The TKI/immune checkpoint inhibitor combinations that have been approved for the treatment of advanced RCC or mRCC are axitinib plus pembrolizumab and axitinib plus avelumab. With no previous data available on the TKI/immune oncology combination at the inception of this study, this was the first study designed to evaluate the safety and efficacy of this combination.
- The current study of pazopanib in combination with pembrolizumab was the first planned exploration designed to assess whether antiangiogenic treatment with pazopanib may potentiate immunotherapy with pembrolizumab in patients with advanced RCC. The combination showed an encouraging efficacy, with an overall CBR of 60%. However, significant hepatotoxicity made this combination unsafe to pursue further.
- This pazopanib plus pembrolizumab trial highlights the importance of well-conducted clinical research and is a cautionary note about the application of PD-1 blockade–based combination therapy. It shows that differences in TKI choice influence tolerability when combined with checkpoint inhibitor therapy. TKI/IO remains a potential option for many patients with mRCC; however, both safety and efficacy need to be balanced in future algorithms.

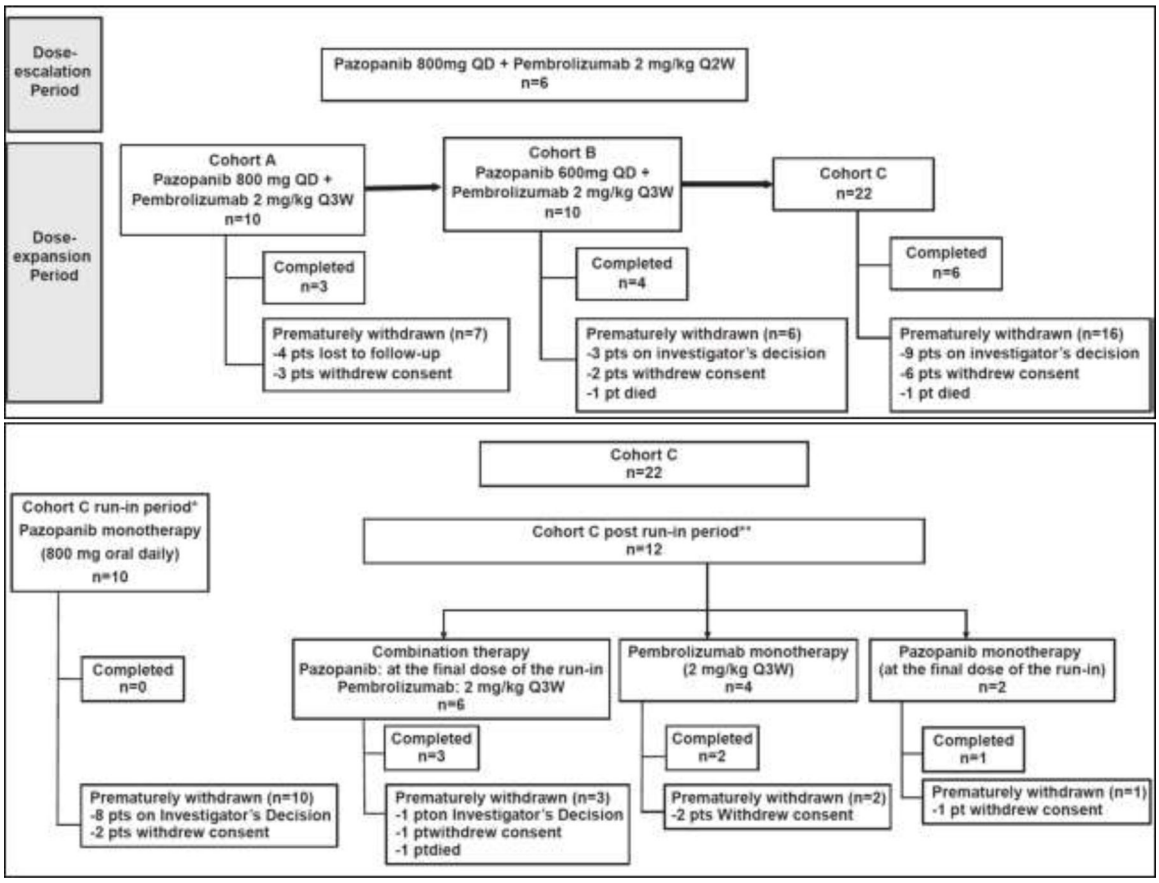

Figure 1.

Patient Dispositions in Different Periods.

Abbreviations: pts = patients; Q2W = once every 2 weeks; Q3W = once every 3 weeks; q.d. = once daily.

*Cohort C run-in period n=10: Patients who entered in the run-in period and did not continue after run-in period. One patient who did not receive treatment, was counted in the Cohort C run-in period. This patient is one of the 8 who prematurely withdrawn from the study following Investigator's decision.

**Cohort C post run-in period n=12: Patients who entered in the run-in period and entered in the post run-in period.

Table 1.

Summary of demographic and baseline disease characteristics – All-treated population

	Cohort A[a] (N=10)	Cohort B[b] (N=10)	Cohort C[c] (N=21)
Age, median, years	61.0	57.0	61.0
Min-max	45–72	46–74	39–77
Sex, n (%)			
Male	5 (50)	7 (70)	15 (71)
Stage at screening, n (%)			
IV	10 (100)	10 (100)	21(100)
Measurable disease at screening, n (%)	10 (100)	10 (100)	21 (100)
Non-target lesion at screening, n (%)	9 (90)	8 (80)	18 (86)
Metastatic disease at screening, n (%)	10 (100)	10 (100)	21 (100)
Prior anticancer radiotherapy, n (%)	0	2 (20)	1 (5)
Any prior nephrectomy, n (%)	9 (90)	9 (90)	18 (86)
Any cancer-related surgeries or procedures, n (%)	2 (20)	6 (60)	3 (14)

[a]Cohort A: Patients treated with the pazopanib 800 mg QD + pembrolizumab 2 mg/kg Q3W combination.

[b]Cohort B: Patients treated with the pazopanib 600 mg QD + pembrolizumab 2 mg/kg Q3W combination.

[c]Cohort C run-in period: Each patient received pazopanib monotherapy at a starting dose of 800 mg orally daily for 9 weeks (pazopanib run-in period); Cohort C post–run-in period: each patient received pembrolizumab monotherapy or combination therapy (before the USM); pembrolizumab monotherapy 2 mg/kg Q3W; or remained on pazopanib monotherapy or continued with the combination therapy (after USM).

max, maximum; min, minimum; Q3W, every 3 weeks; QD, once daily; USM, urgent safety measure.

Table 2.

Overview of AEs for Cohorts A, B, and C – All-treated population

	Cohort A	Cohort B	Cohort C		
	Pazopanib (800 mg QD) + pembrolizumab (2 mg/kg Q3W) (N=10) n (%)	**Pazopanib (600 mg QD) + pembrolizumab (2 mg/kg Q3W) (N=10) n (%)**	**Pazopanib (at the final dose of the run-in) + pembrolizumab (2 mg/kg Q3W) (N=6) n (%)**	**Pembrolizumab (2 mg/kg Q3W) (N=4) n (%)**	**Pazopanib (at the final dose of the run-in) (N=11) n (%)**
Any AE	10 (100)	10 (100)	6 (100)	4 (100)	11 (100)
AEs related to study treatment	10 (100)	10 (100)	6 (100)	4 (100)	11 (100)
Grade 3/4 AEs	9 (90)	9 (90)	6 (100)	2 (50)	6 (55)
AEs leading to permanent discontinuation of study treatment	8 (80)	8 (80)	2 (33)	3 (75)	1 (9)
AEs leading to dose reduction	7 (70)	5 (50)	2 (33)	1 (25)	5 (45)
AEs leading to dose interruption	10 (100)	9 (90)	5 (83)	1 (25)	6 (55)
Any SAE	6 (60)	6 (60)	3 (50)	1 (25)	3 (27)
SAEs related to study treatment	5 (50)	4 (40)	3 (50)	1 (25)	2 (18)
Fatal SAEs	0	1 (10)	0	0	0
Fatal SAEs related to study treatment	0	0	0	0	0

AE, adverse event; Q3W, every 3 weeks; QD, once daily; SAE, serious adverse event.

Table 3.

Summary of AEs for Cohorts A, B, and C – All-treated population

	Cohort A	Cohort B	Cohort C		
AE	**Pazopanib (800 mg QD) + pembrolizumab (2 mg/kg Q3W) (N=10) n (%)**	**Pazopanib (600 mg QD) + pembrolizumab (2 mg/kg Q3W) (N=10) n (%)**	**Pazopanib (at the final dose of the run-in) + pembrolizumab (2 mg/kg Q3W) (N=6) n (%)**	**Pembrolizumab (2 mg/kg Q3W) (N=4) n (%)**	**Pazopanib (at the final dose of the run-in) (N=11) n (%)**
Any event	10 (100)	10 (100)	6 (100)	4 (100)	11 (100)
Nausea	7 (70)	3 (30)	4 (67)	0	8 (73)
Diarrhea	6 (60)	8 (80)	5 (83)	4 (100)	7 (64)
Vomiting	6 (60)	1 (10)	2 (33)	0	7 (64)
Abdominal pain	2 (20)	3 (30)	0	0	0
Constipation	2 (20)	3 (30)	0	2 (50)	2 (18)
Dry mouth	0	4 (40)	0	0	0
Arthralgia	6 (60)	4 (40)	0	2 (50)	0
Pain in extremity	4 (40)	2 (20)	0	0	0
Musculoskeletal chest pain	-	-	2 (33)	0	0
Fatigue	4 (40)	6 (60)	3 (50)	2 (50)	7 (64)
Mucosal inflammation	4 (40)	1 (10)	0	0	0
Chills	0	3 (30)	0	0	0
Pyrexia	0	3 (30)	0	0	0
Upper respiratory tract infection	4 (40)	2 (20)	0	0	0
Sinusitis	3 (30)	0	0	0	0
Alanine aminotransferase increased	7 (70)	7 (70)	2 (33)	4 (100)	5 (45)
Aspartate aminotransferase increased	7 (70)	8 (80)	1 (17)	4 (100)	4 (36)
Lipase increased	6 (60)	4 (40)	4 (67)	1 (25)	0
Amylase increased	3 (30)	3 (30)	2 (33)	1 (25)	0
Blood alkaline phosphatase increased	3 (30)	1 (10)	3 (50)	3 (75)	3 (27)
Headache	6 (60)	4 (40)	0	0	0
Dysgeusia	2 (20)	3 (30)	3 (50)	1 (25)	5 (45)
Dyspnea exertional	4 (40)	1 (10)	3 (50)	0	2 (18)
Oropharyngeal pain	3 (30)	1 (10)	0	0	0
Cough	2 (20)	3 (30)	2 (33)	1 (25)	2 (18)
Pneumonitis			2 (33)	0	0
Pruritus	4 (40)	4 (40)	0	0	0

	Cohort A	Cohort B	Cohort C		
AE	**Pazopanib (800 mg QD) + pembrolizumab (2 mg/kg Q3W) (N=10) n (%)**	**Pazopanib (600 mg QD) + pembrolizumab (2 mg/kg Q3W) (N=10) n (%)**	**Pazopanib (at the final dose of the run-in) + pembrolizumab (2 mg/kg Q3W) (N=6) n (%)**	**Pembrolizumab (2 mg/kg Q3W) (N=4) n (%)**	**Pazopanib (at the final dose of the run-in) (N=11) n (%)**
Rash	2 (20)	5 (50)	0	0	0
Dry skin	1 (10)	3 (30)	0	0	0
Hair color changes	1 (10)	4 (40)	2 (33)	1 (25)	1 (9)
Rash maculopapular	0	3 (30)	0	2 (50)	1 (9)
Hypertension	3 (30)	8 (80)	5 (83)	2 (50)	3 (27)
Hyperglycemia	3 (30)	2 (20)			
Decreased appetite	0	3 (30)	2 (33)	1 (25)	5 (45)

AE, adverse event; Q3W, every 3 weeks; QD, once daily.

Table 4.

Summary of AEs by maximum Grade 3–5 (≥10% of patients in any of the three cohorts) for Cohorts A, B, and C – All-treated population

	Cohort A[a] (N=10) n (%)			Cohort B[b] (N=10) n (%)			Cohort C[c] (N=21) n (%)		
AE	**Grade 3**	**Grade 4**	**Grade 5**	**Grade 3**	**Grade 4**	**Grade 5**	**Grade 3**	**Grade 4**	**Grade 5**
Any event	**7 (70)**	**2 (20)**	**0**	**7 (70)**	**2 (20)**	**1 (10)**	**12 (57)**	**2 (10)**	**0**
Diarrhea	1 (10)	0	0	0	0	0	1 (5)	0	0
Nausea	0	0	0	1 (10)	0	0	1 (5)	0	0
Abdominal pain	0	0	0	1 (10)	0	0	0	0	0
Pathological fracture	1 (10)	0	0	0	0	0	0	0	0
Back pain	0	0	0	1 (10)	0	0	0	0	0
Fatigue	0	0	0	1 (10)	0	0	1 (5)	0	0
Urinary tract infection	0	0	0	1 (10)	0	0	0	0	0
ALT increased	6 (60)	1 (10)	0	4 (40)	1 (10)	0	3 (14)	0	0
AST increased	6 (60)	0	0	5 (50)	0	0	2 (10)	0	0
Lipase increased	5 (50)	1 (10)	0	3 (30)	1 (10)	0	2 (10)	2 (10)	0
Amylase increased	2 (20)	0	0	3 (30)	0	0	1 (5)	0	0
Blood ALP increased	1 (10)	0	0	1 (10)	0	0	1 (5)	0	0
Blood bilirubin increased	1 (10)	0	0	0	0	0	0	0	0
Gamma-glutamyl transferase increased	0	0	0	0	0	0	2 (10)	0	0
Dyspnea	0	0	0	1 (10)	0	0	0	0	0
Pulmonary embolism	0	0	0	1 (10)	0	0	1 (5)	0	0
Rash macular	0	0	0	1 (10)	0	0	0	0	0
Hypertension	2 (20)	0	0	2 (20)	0	0	5 (24)	0	0
Venous thrombosis	0	0	0	1 (10)	0	0	0	0	0
Hyperglycemia	2 (20)	0	0	1 (10)	0	0	0	0	0
Decreased appetite	0	0	0	1 (10)	0	0	1 (5)	0	0
Hypoglycemia	0	0	0	1 (10)	0	0	0	0	0
Atrioventricular block	1 (10)	0	0	0	0	0	0	0	0
Cardiac failure congestive	1 (10)	0	0	0	0	0	0	0	0
Tubulointerstitial nephritis	1 (10)	0	0	0	0	0	0	0	0
Anemia	0	0	0	1 (10)	0	0	0	0	0
Portal vein thrombosis	0	0	0	0	0	1 (10)	0	0	0

[a]Cohort A: Patients treated with the combination therapy: pazopanib (800 mg QD) + pembrolizumab (2 mg/kg Q3W).

[b]Cohort B: Patients treated with the combination therapy: pazopanib (600 mg QD) + pembrolizumab (2 mg/kg Q3W).

[c]Cohort C run-in period: Each patient received pazopanib monotherapy at a starting dose of 800 mg oral daily for 9 weeks (pazopanib run-in period); Cohort C post–run-in period: each patient received pembrolizumab monotherapy or combination therapy (before the USM); pembrolizumab monotherapy 2 mg/kg Q3W; or remained on pazopanib monotherapy or continued with the combination therapy (after USM).

AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Q3W, every 3 weeks; QD, once daily; USM, urgent safety measure.

Table 5.

Summary of AEs related to pazopanib (≥30% of patients in any of the three treatment groups) for Cohorts A, B, and C – All-treated population

	Cohort A	Cohort B	Cohort C		
AEs	**Pazopanib (800 mg QD) + pembrolizumab (2 mg/kg Q3W) (N=10) n (%)**	**Pazopanib (600 mg QD) + pembrolizumab (2 mg/kg Q3W) (N=10) n (%)**	**Pazopanib + pembrolizumab (N=6) n (%)**	**Pembrolizumab (N=4) n (%)**	**Pazopanib (N=11) n (%)**
Any event Diarrhea	10 (100) 6 (60)	10 (100) 6 (60)	6 (100) 5 (83)	4 (100) 2 (50)	11 (100) 6 (55)
Nausea Vomiting	6 (60) 5 (50)	3 (30) 1 (10)	3 (50) 1 (17)	0 0	6 (55) 6 (55)
Fatigue Mucosal inflammation	4 (40) 4 (40)	5 (50) 1 (10)	2 (33) 0	1 (25) 0	4 (36) 0
Alanine aminotransferase increased Aspartate aminotransferase increased	7 (70) 7 (70)	6 (60) 7 (70)	1 (17) 1 (17)	3 (75) 3 (75)	5 (45) 3 (27)
Blood alkaline phosphatase increased Pruritus	3 (30) 3 (30)	0 1 (10)	2 (33) 0	2 (50) 0	2 (18) 0
Rash Hair color changes	2 (20) 1 (10)	3 (30) 4 (40)	0 2 (33)	0 1 (25)	0 1 (9)
Rash maculopapular Hypertension	0 3 (30)	3 (30) 7 (70)	0 3 (50)	0 0	0 1 (9)
Dysgeusia	-	-	2 (33)	1 (25)	4 (36)

AE, adverse event; Q3W, every 3 weeks; QD, once daily.

Table 6.

Summary of AEs related to pembrolizumab for Cohorts A, B, and C – All-treated population

	Cohort A	Cohort B	Cohort C	
AEs	**Pazopanib (800 mg QD) + pembrolizumab (2 mg/kg Q3W) (N=10) n (%)**	**Pazopanib (600 mg QD) + pembrolizumab (2 mg/kg Q3W) (N=10) n (%)**	**Pazopanib + pembrolizumab (N=6) n (%)**	**Pembrolizumab (N=4) n (%)**
Any event	10 (100)	10 (100)	0	0
Aspartate aminotransferase increased Alanine aminotransferase increased	7 (70) 6 (60)	6 (60) 5 (50)	0 0	0 0
Lipase increased Diarrhea	0 5 (50)	0 3 (30)	2 (33) 2 (33)	1 (25) 2 (50)
Arthralgia Pneumonitis	0 0	0 0	0 2 (33)	2 (50) 0

AE, adverse event; Q3W, every 3 weeks; QD, once daily.

Table 7.

Summary of exposure to pazopanib for Cohorts A, B, and C – All-treated population

		Cohort A	Cohort B	Cohort C		
		Pazopanib (800 mg QD) + pembrolizumab (2 mg/kg Q3W) (N=10)	**Pazopanib (600 mg QD) + pembrolizumab (2 mg/kg Q3W) (N=10)**	**Pazopanib (at the final dose of the run-in) + pembrolizumab (2 mg/kg Q3W) (N=6) n (%)**	**Pembrolizumab (2 mg/kg Q3W) (N=4) n (%)**	**Pazopanib (at the final dose of the run-in) (N=11) n (%)**
Patient daily dose (mg) [a]	Mean (SD)	568.4 (224.52)	503.9 (120.26)	610.7 (189.43)	706.3 (187.50)	691.6 (110.36)
	Median Min-max	586.9 238–800	556.6 265–600	610.9 335–800	800.0 425–800	688.4 538–800
Time on study treatment (months) [b]	Mean (SD) Median	8.0 (7.43) 4.4	10.5 (13.29) 3.3	12.3 (8.32) 11.4	1.8 (0.19) 1.9	2.0 (1.15) 1.9
	Min-max <3 months	1–23 3 (30)	1–41 5 (50)	4–25 0	2–2 4 (100)	0–4 9 (82)
Time on study treatment categories, n (%)	3 to <6 months 6 to <12 month s	3 (30) 1 (10)	1 (10) 1 (10)	2 (33) 1 (17)	0 0	2 (18) 0
	12 to <18 months ≥18 months	2 (20) 1 (10)	0 3 (30)	2 (33) 1 (17)	0 0	0 0

[a]The patient daily dose (the cumulative dose divided by the duration of exposure) was calculated for each patient first, and the summary statistics were calculated based on the patient's average daily dose.

[b]The time on study drug does not exclude dose interruptions.

max, maximum; min, minimum; Q3W, every 3 weeks; QD, once daily; SD, standard deviation.

Table 8.

Summary of investigator-assessed best confirmed response for Cohorts A, B, and C (RECIST 1.1 criteria) – All-treated population

	Cohort A	Cohort B	Cohort C		
	Pazopanib (800 mg QD) + pembrolizumab (2 mg/kg Q3W) (N=10) n (%)	**Pazopanib (600 mg QD) + pembrolizumab (2 mg/kg Q3W) (N=10) n (%)**	**Pazopanib (at the final dose of the run-in) + pembrolizumab (2 mg/kg Q3W) (N=6) n (%)**	**Pembrolizumab (2 mg/kg Q3W) (N=4) n (%)**	**Pazopanib (at the final dose of the run-in) (N=11) n (%)**
Best response					
CR	2 (20)	1 (10)	0	1 (25)	0
PR	4 (40)	1 (10)	2 (33)	0	0
SD	4 (40)	7 (70)	3 (50)	2 (50)	6 (55)
PD	0	1 (10)	1 (17)	1 (25)	0
Overall response rate					
CR + PR	6 (60)	2 (20)	2 (33)	1 (25)	0
95% CI[a]	(26.2, 87.8)	(2.5, 55.6)	(4.3, 77.7)	(0.6, 80.6)	(0.0, 28.5)
Clinical benefit rate					
CR or PR or ≥6-month SD	6 (60)	6 (60)	3 (50)	2 (50)	0
95% CI[a]	(26.2, 87.8)	(26.2, 87.8)	(11.8, 88.2)	(6.8, 93.2)	(0.0, 28.5)
18-month PFS rate (95% CI) [b]	0.56 (0.22, 0.96)	0.88 (0.28, 0.99)	0.20 (0.01, 0.72)	0.50 (0.16, 1.00)	1.00 (0.72, 1.00)

[a]The 95% exact binomial CI (Clopper and Pearson, 1934) was calculated using the FREQ procedure (with the EXACT statement).

[b]The 95% exact binomial CI (Clopper and Pearson, 1934) was calculated using the FREQ procedure (with the EXACT statement).

CI, confidence interval; CR, complete response; PD, progressive disease; PFS, progression-free survival; PR, partial response; Q3W, every 3 weeks; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumours; SD, stable disease.