Surufatinib Plus Toripalimab in Patients with Advanced Solid Tumors: A Single-Arm, Open-Label, Phase 1 Trial

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Research

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Abstract

Background

Preclinical studies have supported a potential synergistic antitumor activity between surufatinib and anti-programmed death ligand-1 (PD-L1). We describe here the results of a single-arm, open-label phase 1 trial to evaluate the safety, preliminary efficacy, and pharmacokinetics (PK) in patients with advanced solid tumors treated with surufatinib combined with toripalimab, an inhibitor of PD-L1.

Methods

This is an open-label, dose escalation and expansion study in patients with solid tumors who had failed standard therapies or had no effective treatment. In the dose escalation stage, 3 cohorts of patients were treated with surufatinib, at dose levels of 200, 250, or 300 mg once daily (QD) in combination with a fixed dose of toripalimab 240 mg, every 3 weeks (Q3W), to evaluate maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D). Additional patients were enrolled in the dose expansion phase to further assess the efficacy, safety, and PK profile.

Results

From April 1, 2019 to July 10, 2020, 31 patients were screened, of which 28 patients were enrolled. One patient in the 300 mg cohort experienced dose limited toxicity (DLT), a grade 3 hyperthyroidism. The top 3 most common treatment-related adverse events of $\geq$ grade 3 were transaminases increased (17.9%), hypertension (14.3%) and blood bilirubin increased (10.7%). No treatment-related death or treatment discontinuation was identified. The RP2D was determined to be surufatinib 250 mg QD plus toripalimab 240 mg Q3W. Overall objective response rate was 22.2% [95% confidential interval (CI) 8.6–42.3], and disease control rate reached 81.5% (95% CI 61.9–93.7).

Conclusions

Surufatinib plus toripalimab was well-tolerated, with no unexpected safety signals, and showed promising antitumor activity in patients with advanced solid tumors.

Trial registration

clinicaltrials.gov, NCT03879057; Registered March 18, 2019,
<https://clinicaltrials.gov/ct2/show/NCT03879057>

Background

During the past several years, immune checkpoint inhibitors (ICIs), such as antibodies against programmed death protein-1 (PD-1) and programmed death ligand-1 (PD-L1), have shown impressive clinical benefits in the treatment of solid tumors [1–4]. However, although PD-1/PD-L1 antibodies have shown enhanced

effectiveness in patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) status, efficacy of single agent PD-1/PD-L1 inhibitors in microsatellite stable/ mismatch repair proficient (MSS/pMMR) patients has not been satisfactory [5–7].

Attempts at increasing efficacy have been made using different combinations with ICIs. Preclinical evidence suggests that the combination of vascular endothelial growth factor/ vascular endothelial growth factor receptor (VEGF/VEGFR) inhibitors and PD-1/PD-L1 inhibitors could increase the anti-tumor activity, by provoking T cell function and modulating suppressive immune cells as well as the stroma, in the tumor microenvironment [8–9]. The use of VEGF/VEGFR therapy could promote the extravasation and migration of immune inflammatory cells, thus enhancing the immune inflammatory response after the application of immunotherapy drugs, increasing the drugs' aggressiveness against tumor cells and thereby improving the efficacy of immunotherapy drugs [10]. This notion is supported by mounting evidence in recent years, demonstrating the clinical benefits of VEGF/VEGFR therapy combined with immunotherapy for patients with advanced solid tumors [11–16].

In particular, the combination of VEGF/VEGFR inhibitor with an inhibitor of PD-1 has been shown to be effective for treatment of a number of different solid tumors. A study using lenvatinib, a VEGFR inhibitor, plus pembrolizumab, an antibody against PD-1, elicited an objective response rate (ORR) of 63% in patients with renal clear cell carcinoma. Among the treatment-naïve patients in this study, the ORR reached 83%, and the disease control rate (DCR) was 100% [14]. In addition, recent results of the REGONIVO study, another combination of VEGF/VEGFR and PD-1 inhibitors, regorafenib and nivolumab, respectively, showed promising efficacy in the treatment of MSS gastric cancer and colorectal cancer [17].

Surufatinib is a small molecule kinase inhibitor that primarily acts on VEGFR 1, 2, 3, fibroblast growth factor receptor 1 (FGFR 1), and colony stimulating factor 1 receptor (CSF-1R). Surufatinib has demonstrated clinical efficacy in several solid tumors [18–19]. Toripalimab is a recombinant humanized monoclonal immunoglobulin G4 (IgG4) antibody with a hinge S228P mutation that specifically targets PD-1, which has also shown efficacy in the treatment of solid tumors [20–22]. Preclinical studies have demonstrated that surufatinib decreased M2 tumor-associated macrophages (TAMs) and increased M1 TAMs, and this immune-modulation effect might result in enhanced anti-tumor effect when surufatinib combines with anti-PD-1/PD-L1 antibody [23]. Here we report the results of a phase 1 study of surufatinib combined with toripalimab in the treatment of patients with advanced solid tumors.

Methods

Study design and participants

This study is an open-label, dose escalation, and dose expansion trial conducted in Peking University Cancer Hospital, Beijing, China. All patients enrolled had unresectable or metastatic advanced solid tumors that were histologically or cytologically confirmed. Patients were 18–75 years old, had failed standard treatment (due to disease progression after the treatment or intolerable toxicity or side effects

during the treatment) or had not responded to currently available therapies. Enrolled patients had physical performance score 0–1 [Eastern Cooperative Oncology Group performance status (ECOG PS) score]. Patients with hepatocellular carcinoma had Child-Pugh A or B7 hepatic function. Patients also had measurable target lesions [per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1], adequate bone marrow function and liver function, an expected survival time of more than 12 weeks. Patients who experienced unrecovered anti-tumor treatment-related toxicity or had other malignant diagnosis, central nervous system (CNS), or brain metastases were excluded. Detailed inclusion and exclusion criteria were available in Supplementary Table S1.

This clinical trial was approved by Ethics Committee of Peking University Cancer Hospital and was conducted strictly in accordance with the Declaration of Helsinki and Good Clinical Practice. All patients provided written informed consent form (ICF) before enrollment. The study was registered at ClinicalTrials.gov with registration number NCT03879057.

Procedures

All patients enrolled in this study received the treatment every 3 weeks in 1 cycle. In the dose escalation phase, a “3 + 3” design was applied. Patients were assigned to 1 of the 3 surufatinib dose cohorts and received surufatinib 200, 250, or 300 mg orally once daily (QD) in combination with a fixed dose of toripalimab (240 mg intravenously) every 3 weeks (Q3W) to evaluate the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D). Dose limited toxicity (DLT) assessment was performed within 28 days of the first dose.

In the dose expansion phase, additional patients were enrolled into the 3 dose cohorts to assess the efficacy, safety, and pharmacokinetic (PK) profile. All patients received treatment until the first occurrence of disease progression, death, intolerable toxicity, or completion of the study. The dose of surufatinib could be adjusted according to the dose adjustment principle; however, dose reduction was not allowed for toripalimab.

Tumor assessments (per RECIST v1.1) were performed once every 6 weeks (± 7 days) from administration of the first dose, and once every 12 weeks (± 7 days) after 48 weeks of the treatment until disease progression, death, intolerable toxicity, or fulfillment of other criteria for terminating the study treatment, whichever occurred first. Patients were followed every 12 weeks (± 7 days) after discontinuation of the treatment to record their survival status until death, lost to follow-up, or withdrawal of informed consent, whichever occurred first.

Pharmacokinetic blood samples were collected for PK evaluations at multiple time points on Cycle 1 Day 1, Cycle 2 Day 1 and Cycle 3 Day 1 for surufatinib and toripalimab, respectively.

For patients who signed an optional biomarker ICF, additional tumor samples were collected to evaluate the correlation between the efficacy of surufatinib and/or toripalimab and PD-L1 expression. PD-L1 expression was detected by immunohistochemistry staining with SP263 antibody using a Ventana (Tucson, AZ) autostainer [24]. Positive PD-L1 expression was defined as the presence of membrane

staining of any intensity in $\geq 1\%$ tumor cells or in tumor-infiltrating immune cells in tumor area occupied by tumor cells, intratumoral cells and peritumoral stroma.

Outcomes

The primary objective was to evaluate the safety and tolerability of surufatinib combined with toripalimab in patients with advanced solid tumors, and to determine DLT, MTD, and RP2D.

The secondary objectives were to evaluate the preliminary efficacy (per RECIST v1.1) and PK profile of surufatinib, combined with toripalimab, in patients with advanced solid tumors.

The exploratory objective was to evaluate potential biomarkers that predict the efficacy of surufatinib and/or toripalimab.

Statistical analysis

All safety analyses, progression-free survival (PFS) and overall survival (OS) statistics were based on the safety population, including patients who received at least 1 dose of any study drug. DLT events were based on the DLT evaluable population, including patients who received at least 1 cycle of treatment and completed all safety assessments within the DLT assessment window or discontinued early due to DLT. All efficacy endpoints, excluding PFS and OS, were analyzed based on the efficacy evaluable population, including all patients who received at least 1 dose of any study drug and had tumor assessment at baseline and post drug administration prior to initiation of new anti-cancer therapies. The PK analysis was based on the PK population, which included all patients who received at least one dose of the study drug, had at least one PK sample collected and analyzed, and had no protocol deviation that might affect the PK data.

Two-sided 95% CI of ORR and DCR were computed using the Exact (Clopper-Pearson) method. For time-to-event variables [PFS, OS, DoR (duration of response) and TTR (time to response)], median event time as well as the corresponding 95% CI were estimated using Kaplan-Meier method. All statistical analyses were performed using SAS 9.4 software. Adverse events (AEs) were graded by NCI CTCAE (Common Terminology Criteria for Adverse Events) v4.03, and coded using the Medical Dictionary for Regulatory Activities (MedDRA) v21.1. Treatment-related AEs (TRAEs) referred to AEs related to surufatinib or toripalimab, which were judged by the investigators. PK parameters were calculated by non-compartmental analysis using Phoenix WinNonlin Version 8.0. The PK parameters included maximum observed concentration ($C_{\max}$), time to $C_{\max}$ ($T_{\max}$) and area under the concentration-time curve for a dosing interval ($AUC_{0-\tau}$). All calculations of the parameters were based on actual sampling times.

Results

From April 1, 2019 to July 10, 2020 (cutoff date), 31 patients were screened, and 28 were enrolled, including 4 in 200 mg cohort, 12 in 250 mg cohort, and 12 in 300 mg cohort, respectively. By the data cutoff, 6 patients (21.4%) were still on study treatment, including 5/12 patients (41.7%) in the 250 mg

cohort, and 1/12 patients (8.3%) in the 300 mg cohort. Twenty-two of the 28 patients (78.6%) had discontinued study treatment at cutoff date; most of these study treatment discontinuations were due to disease progression (17 patients).

Baseline characters

Demographic and baseline characteristics are shown in Table 1. Most enrolled patients [22/28 patients (78.6%)] were male, and all patients (100%) presented with stage IV tumors at screening. Cancer types included neuroendocrine neoplasm [NEN; 19/28 patients (67.9%)], colorectal cancer [CRC; 4/28 patients (14.3%)], esophageal squamous cell carcinoma [EC; 2/28 patients (7.1%)], gastric adenocarcinoma [GC; 2/28 patients (7.1%)] and metastatic squamous cell carcinoma [1/28 patients (3.6%)]. The majority of enrolled NEN patients had neuroendocrine carcinoma [NEC; 11/28 patients (39.3%)], and the remaining 8 patients had neuroendocrine tumor (NET) (4 patients with NET G2 and 4 patients with NET G3).

Table 1
Patient demographics and baseline characteristics (safety population)

	Surufatinib 200 mg QD + Toripalimab 240 mg Q3W (N= 6) n (%)	Surufatinib 250 mg QD + Toripalimab 240 mg Q3W (N= 12) n (%)	Surufatinib 300 mg QD + Toripalimab 240 mg Q3W (N= 12) n (%)	Total (N= 30) n (%)
Age (Years)				
Mean (standard deviation)	55.2(13.59)	56.1(13.92)	59.3(7.69)	57.2(11.44)
Median	57.0	61.5	61.5	61.0
Min, Max	36, 74	30, 71	45, 68	30, 74
Sex, n (%)				
Male	5 (83.3)	10 (83.3)	9 (75.0)	24 (80.0)
Female	1 (16.7)	2 (16.7)	3 (25.0)	6 (20.0)
Childbearing potential^a				
Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No	1 (100.0)	2 (100.0)	3 (100.0)	6 (100.0)
Race, n(%)				
Asian	6 (100.0)	12 (100.0)	12 (100.0)	30 (100.0)
Non-Asian	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Height (cm)				
Mean (standard deviation)	169.50(8.216)	167.50(10.553)	168.63(6.050)	168.35(8.268)
Median	168.50	167.50	169.50	169.00
Min, Max	161.0, 180.0	147.0, 187.0	156.0, 175.0	147.0, 187.0
Weight (kg)				

BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; PS, performance status; CRC, colorectal cancer; EC, esophageal squamous cell carcinoma; GC, gastric cancer; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor.

¹Site of primary tumor was only collected for patients with NEC.

	Surufatinib 200 mg QD + Toripalimab 240 mg Q3W (N= 6) n (%)	Surufatinib 250 mg QD + Toripalimab 240 mg Q3W (N= 12) n (%)	Surufatinib 300 mg QD + Toripalimab 240 mg Q3W (N= 12) n (%)	Total (N= 30) n (%)
Mean (standard deviation)	60.50(15.202)	71.63(16.205)	62.50(10.002)	65.75(14.204)
Median	59.00	69.75	60.50	61.75
Min, Max	40.0, 82.0	50.0, 98.0	49.0, 81.0	40.0, 98.0
BMI (kg/m²)				
Mean (standard deviation)	20.83(3.816)	25.46(4.998)	21.93(2.918)	23.12(4.375)
Median	20.70	24.50	21.60	22.30
Min, Max	15.4, 25.3	18.3, 36.9	16.3, 27.7	15.4, 36.9
Baseline ECOG PS, n (%)				
0	2 (33.3)	3 (25.0)	6 (50.0)	11 (36.7)
1	4 (66.7)	9 (75.0)	6 (50.0)	19 (63.3)
Cancer type, n (%)				
CRC	0 (0.0)	3 (25.0)	1 (8.3)	4 (13.3)
EC	0 (0.0)	1 (8.3)	1 (8.3)	2 (6.7)
GC	0 (0.0)	0 (0.0)	2 (16.7)	2 (6.7)
NEN	6 (100.0)	7 (58.3)	8 (66.7)	21 (70.0)
NEC	3 (50.0)	5 (41.7)	5 (41.7)	13 (43.3)
NET G2	0 (0.0)	1 (8.3)	3 (25.0)	4 (13.3)
NET G3	3 (50.0)	1 (8.3)	0 (0.0)	4 (13.3)
Metastatic squamous cell carcinoma	0 (0.0)	1 (8.3)	0 (0.0)	1 (3.3)

BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; PS, performance status; CRC, colorectal cancer; EC, esophageal squamous cell carcinoma; GC, gastric cancer; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor.

¹Site of primary tumor was only collected for patients with NEC.

	Surufatinib 200 mg QD + Toripalimab 240 mg Q3W (N= 6) n (%)	Surufatinib 250 mg QD + Toripalimab 240 mg Q3W (N= 12) n (%)	Surufatinib 300 mg QD + Toripalimab 240 mg Q3W (N= 12) n (%)	Total (N= 30) n (%)
Site of primary tumor¹, n (%)				
Colon	0 (0.0)	0 (0.0)	1 (8.3)	1 (3.3)
Esophagus	0 (0.0)	0 (0.0)	1 (8.3)	1 (3.3)
Stomach/Gastroesophageal junction	2 (33.3)	3 (25)	1 (8.3)	6 (20)
Lung	0 (0.0)	1 (8.3)	0 (0.0)	1 (3.3)
Pancreas	2 (33.3)	1 (8.3)	1 (8.3)	4 (13.3)
Rectum	2 (33.3)	0 (0.0)	2 (16.7)	4 (13.3)
Other	0 (0.0)	1 (8.3)	2 (16.7)	3 (10.0)
Time from initial diagnosis to first dose of study drug(months)				
Mean (standard deviation)	17.17(5.819)	16.88(8.253)	24.69(20.607)	20.06(14.406)
Median	16.89	16.39	21.72	18.28
Min, Max	11.4, 26.5	4.9, 37.2	3.0, 70.4	3.0, 70.4
Tumor stage at screening, n (%)				
I	6 (100.0)	12 (100.0)	12(100)	30 (100)
BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; PS, performance status; CRC, colorectal cancer; EC, esophageal squamous cell carcinoma; GC, gastric cancer; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor.				
¹ Site of primary tumor was only collected for patients with NEC.				

Safety

Thirteen patients were included in the DLT evaluable population, among whom 1 patient in the 300 mg cohort reported a DLT event, a grade 3 hyperthyroidism which was deemed related to toripalimab.

At data cutoff, 28 patients were included in the safety population. All patients had at least 1 TRAE of any grade. Of the 28 patients, 14 (50%) experienced 1 or more $\geq$ grade 3 TRAE. The most common ($\geq$ 5% incidence) $\geq$ grade 3 TRAE included transaminase increased [5 patients (17.9%) (1 patient in the 200 mg cohort and 4 patients in the 300 mg cohort)], hypertension [4 patients (14.3%) (2 patients in the 250 mg cohort and 2 patients in 300 mg cohort)], blood bilirubin increased [3 patients (10.7%) in the 300 mg cohort], vomiting [2 patients (7.1%) in the 300 mg cohort], and asthenia [2 patients (7.1%) in the 300 mg cohort] (Table 2).

Table 2
Summary of treatment-related AEs (safety population)*

	Surufatinib 200 mg QD + Toripalimab 240 mg Q3W (<i>N</i> = 6) n(%)		Surufatinib 250 mg QD + Toripalimab 240 mg Q3W (<i>N</i> = 12) n(%)		Surufatinib 300 mg QD + Toripalimab 240 mg Q3W (<i>N</i> = 12) n(%)		Total (<i>N</i> = 30) n(%)	
Preferred Term	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Subjects with any treatment-related AE	6 (100.0)	1 (16.7)	12 (100.0)	4 (33.3)	12 (100.0)	9 (75.0)	30 (100.0)	14 (46.7)
Proteinuria ¹	6 (100.0)	0 (0.0)	9 (75.0)	0 (0.0)	11 (91.7)	0 (0.0)	26 (86.7)	0 (0.0)
Fecal occult blood positive ²	5 (83.3)	0 (0.0)	8 (66.7)	0 (0.0)	10 (83.3)	0 (0.0)	23 (76.7)	0 (0.0)
Blood bilirubin increased ³	5 (83.3)	0 (0.0)	8 (66.7)	0 (0.0)	9 (75.0)	3 (25.0)	22 (73.3)	3 (10.0)
Hypothyroidism	3 (50.0)	0 (0.0)	6 (50.0)	0 (0.0)	11 (91.7)	0 (0.0)	20 (66.7)	0 (0.0)
Hypertension ⁴	5 (83.3)	0 (0.0)	3 (25.0)	2 (16.7)	8 (66.7)	2 (16.7)	16 (53.3)	4 (13.3)
Blood urine present ⁵	1 (16.7)	0 (0.0)	7 (58.3)	0 (0.0)	8 (66.7)	0 (0.0)	16 (53.3)	0 (0.0)
Transaminases increased ⁶	3 (50.0)	1 (16.7)	3 (25.0)	0 (0.0)	7 (58.3)	4 (33.3)	13 (43.3)	5 (16.7)
White blood cell count decreased	4 (66.7)	0 (0.0)	3 (25.0)	0 (0.0)	6 (50.0)	0 (0.0)	13 (43.3)	0 (0.0)
Anaemia ⁷	0 (0.0)	0 (0.0)	3 (25.0)	1 (8.3)	8 (66.7)	1 (8.3)	11 (36.7)	1 (6.7)
Hyperthyroidism	2 (33.3)	0 (0.0)	1 (8.3)	0 (0.0)	4 (33.3)	1 (8.3)	7 (23.3)	1 (3.3)
Amylase increased	2 (33.3)	0 (0.0)	4 (33.3)	0 (0.0)	2 (16.7)	1 (8.3)	8 (26.7)	1 (3.3)
Blood urea increased	0 (0.0)	0 (0.0)	4 (33.3)	0 (0.0)	3 (25.0)	0 (0.0)	7 (23.3)	0 (0.0)
Neutrophil count decreased	2 (33.3)	0 (0.0)	1 (8.3)	0 (0.0)	4 (33.3)	0 (0.0)	7 (23.3)	0 (0.0)

	Surufatinib 200 mg QD + Toripalimab 240 mg Q3W (N = 6) n(%)		Surufatinib 250 mg QD + Toripalimab 240 mg Q3W (N = 12) n(%)		Surufatinib 300 mg QD + Toripalimab 240 mg Q3W (N = 12) n(%)		Total (N= 30) n(%)	
Blood creatine phosphokinase increased	1 (16.7)	0 (0.0)	1 (8.3)	0 (0.0)	4 (33.3)	1 (8.3)	6 (20.0)	1 (3.3)
Blood creatine phosphokinase MB increased	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)	5 (41.7)	0 (0.0)	6 (20.0)	0 (0.0)
Vomiting	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)	3 (25.0)	2 (16.7)	4 (13.3)	2 (6.7)
Asthenia	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (16.7)	2 (16.7)	3 (10.0)	2 (6.7)
*Treatment-related AEs of any grade occurring in $\geq 20\%$ of total patients or treatment-related grade 3 or worse AEs occurring in $\geq 5\%$ of total patients (safety population).								
AE, adverse event.								
¹ Proteinuria included proteinuria and protein urine present.								
² Fecal occult blood positive included fecal occult blood positive, occult blood positive and occult blood.								
³ Blood bilirubin increased included blood bilirubin increased, total bilirubin increased, direct bilirubin increased, indirect bilirubin increased and bilirubin increased.								
⁴ Hypertension included hypertension and blood pressure increased.								
⁵ Blood urine present included blood urine present and red blood cells urine positive.								
⁶ Transaminases increased included transaminases increased, alanine aminotransferase increased and aspartate aminotransferase increased.								
⁷ Anaemia included anaemia and haemoglobin decreased.								

Five (17.9%) patients experienced treatment-related serious adverse events (SAEs), most of which were observed in the 300 mg cohort [4/12 patients (33.3%)]; the remaining 1 patient (8.3%) was in the 250 mg cohort. No fatal treatment-related SAE was reported.

TRAE caused dose interruption or dose reduction in 15 patients (53.6%), with a frequency of 58.3% (7/12 patients) in 300 mg cohort, which is a similar with incidence from the other 2 cohorts (50.0% for the 200 and 250 mg cohort, respectively). There was no TRAE that led to treatment discontinuation in this study.

The incidence of immune-related AE was 82.1% in the safety population and was comparable among all dose cohorts (75.0% in the 200 mg cohort and 83.3% in each of the 250 mg and 300 mg cohorts). Adverse events of special interest of any grade occurred in 22/28 patients (78.6%), of which blood bilirubin increased occurred with the highest frequency [20/28 patients (71.4%)].

Pharmacokinetics

The PK parameters of surufatinib were available for 28 patients for Cycle 1 Day 1, 25 patients for Cycle 2 Day 1, and 21 patients for Cycle 3 Day 1. At each dose level of surufatinib, the $AUC_{0-\tau}$ on Cycle 2 Day 1 was higher than those on the other sampling days. Following the first cycle of dosing, the mean of accumulation ratio based on $AUC_{0-\tau}$ was 1.8, 2.0 and 2.1 for 200 mg, 250 mg, and 300 mg, respectively. The number of patients for the toripalimab PK analysis was 28, 23 and 21 for Cycle 1 Day 1, Cycle 2 Day 1, and Cycle 3 Day 1, respectively. In spite of the different dose levels of concomitant surufatinib, the toripalimab exposure ($AUC_{0-\tau}$) was similar on each sampling day. The $AUC_{0-\tau}$ on Cycle 3 Day 1 was higher than those on the other sampling days. The mean of accumulation ratio was 1.3 to 1.4 following the first dosing and 1.3 to 1.6 following the second dosing. The major PK parameters of surufatinib and toripalimab are listed in Table 3.

Table 3
PK parameters of surufatinib and toripalimab (PK population)

Surufatinib							
Dose (mg)		Day	N	C _{max} (ng/mL)	T _{max} (h)		AUC _{0-τ} (h × ng/mL)
Surufatinib	Toripalimab			Geometric mean (CV%)	Median	min, max	Geometric mean (CV%)
200	240	C1D1	6	277 (27.9)	1.98	1.08, 4.00	1845 (8.53)
250	240	C1D1	12	289 (58.3)	1.58	1.00, 4.00	1845 (54.3)
300	240	C1D1	12	228 (46.3)	2.00	1.10, 4.00	1878 (72.4)
200	240	C2D1	6	268 (55.0)	2.97	1.90, 4.00	3013 (42.6)
250	240	C2D1	11	407 (71.4)	2.00	1.00, 4.03	3610 (68.0)
300	240	C2D1	10	281 (34.0)	2.97	1.00, 7.93	3668 (30.4)
200	240	C3D1	3	239 (53.6)	1.98	1.98, 4.00	2298 (24.3)
250	240	C3D1	9	310 (58.8)	1.93	1.00, 4.00	2398 (52.3) ¹
300	240	C3D1	10	361 (31.7)	2.00	1.90, 4.10	3496 (30.1)
Toripalimab							
Dose (mg)		Day	N	C _{max} (μg/mL)	T _{max} (h)		AUC _{0-τ} (h × μg/mL)
Surufatinib	Toripalimab			Geometric mean (CV%)	Median	min, max	Geometric mean (CV%)
200	240	C1D1	6	78.1 (15.2)	1.96	0.78, 6.63	15925 (22.8)
250	240	C1D1	12	71.4 (21.6)	1.85	1.03, 24.4	14142 (25.6)

C: Cycle; D: Day; PK, pharmacokinetics; C_{max}, maximum observed concentration; T_{max}, time to C_{max}; AUC_{0-τ}, area under the concentration-time curve for a dosing interval; CV, coefficient of variation.

¹N for AUC_{0-τ} in C3D1 was eight.

Surufatinib							
300	240	C1D1	12	81.2 (24.5)	1.12	0.70, 6.78	16458 (25.0)
200	240	C2D1	4	96.2 (17.9)	2.63	1.32, 6.63	21512 (26.4)
250	240	C2D1	11	83.8 (24.5)	1.13	0.62, 6.68	17176 (31.5)
300	240	C2D1	10	98.1 (27.5)	1.26	0.63, 24.2	20660 (33.7)
200	240	C3D1	3	110 (29.0)	1.45	0.98, 2.72	24626 (34.9)
250	240	C3D1	10	97.4 (25.0)	1.87	0.58, 24.2	20157 (39.5)
300	240	C3D1	9	103 (33.2)	1.17	0.72, 24.2	20063 (46.6)
C: Cycle; D: Day; PK, pharmacokinetics; C _{max} , maximum observed concentration; T _{max} , time to C _{max} ; AUC _{0-τ} , area under the concentration-time curve for a dosing interval; CV, coefficient of variation.							
¹ N for AUC _{0-τ} in C3D1 was eight.							

Preliminary efficacy

Twenty-seven of 28 enrolled patients were evaluable for tumor response. By the data cutoff, there were 6 patients with a partial response (PR) and 16 patients with stable disease (SD) confirmed as their best overall response (BOR) among the evaluable patients. Most of the patients with PR (5/6 patients) were from the 250 mg cohort, except for 1 patient in the 300 mg cohort. The overall ORR and DCR were 22.2% and 81.5%, respectively. The ORR in the 200 mg, 250 mg, and 300 mg cohorts was 0%, 45.5%, and 8.3% respectively; the DCR was 50.0%, 100%, and 75.0% respectively (Table 4).

Table 4
Tumor response of surufatinib plus toripalimab (efficacy evaluable population)

	Surufatinib 200 mg QD + Toripalimab 240 mg Q3W (N= 6) n (%)	Surufatinib 250 mg QD + Toripalimab 240 mg Q3W (N= 11) n (%)	Surufatinib 300 mg QD + Toripalimab 240 mg Q3W (N= 12) n (%)	Total (N= 29) n (%)
Confirmed best overall response (based on RECIST v1.1)				
CR	1 (16.7)	0 (0.0)	0 (0.0)	1 (3.4)
PR	0 (0.0)	5 (45.5)	1 (8.3)	6 (20.7)
SD	2 (33.3)	6 (54.5)	8 (66.7)	16 (55.2)
PD	3 (50.0)	0 (0.0)	3 (25.0)	6 (20.7)
ORR¹	1 (16.7)	5 (45.5)	1 (8.3)	7 (24.1)
95% CI of ORR	0.4–64.1	16.7–76.6	0.2–38.5	10.3–43.5
DCR²	3 (50.0)	11 (100.0)	9 (75.0)	23 (79.3)
95% CI of DCR	11.8–88.2	71.5–100.0	42.8–94.5	60.3–92.0
CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate. CI, confidential interval; RECIST, Response Evaluation Criteria in Solid Tumors.				
¹ ORR was defined as the proportion of patients with confirmed best overall response of CR or PR.				
² DCR was defined as the proportion of patients with best overall response of CR or PR or SD.				

Decrease in target lesion size was observed in 16 patients (59.3%), most of whom were in the 250 mg cohort (9 patients). There were 4 patients with PR with response trends that were continuing at the cutoff date (Fig. 1B, 1C).

Four of the 18 evaluable NENs patients achieved an objective response, including 2 PR in patients with NEC, and 2 PR in patients with NET G2. For the remaining NEN patients, 11 patients had SD, including 2 patients in the 200 mg cohort, 3 patients in the 250 mg cohort, and 6 patients in the 300 mg cohort.

A response of SD or better was seen in all 4 CRC patients, 1 patient with PR (MSI-H, 250 mg cohort), and 3 patients with SD (all MSS, 2 patients in the 250 mg cohort, 1 patient in the 300 mg cohort).

At the data cutoff, tumor progression or death was observed in 21 patients (maturity of PFS data, 75.0%), and overall median PFS (mPFS) was 4.0 months (95% CI 2.6–5.5). The mPFS was 1.9 months (95% CI 1.2–not reached) for the 200 mg cohort, 5.5 months (95% CI 2.7–not reached) for the 250 mg cohort, and 4.1 months (95% CI 1.2–9.5) for the 300 mg cohort (Supplementary Figure S1). The overall 6-month PFS rate was 28.7% (95% CI 12.8%, 46.8%). Median DoR, TTR, and OS were not reached at the cutoff date, and the overall 6-month OS rate was 78.0% (95% CI, 57.4%, 89.5%).

Biomarker Analysis

Tumor tissues from 25 patients at baseline were available for PD-L1 expression analysis. Among the 12 PD-L1 positive patients, 4/12 patient (33.3%) achieved PR, while 6/12 (50.0%) reported SD. In the 13 patients with negative PD-L1 status, 10/13 (76.9%) achieved their BOR as SD or better, including 2/13 patients (15.4%) with PR, and 8/13 patients (61.5%) with SD (Supplementary Table S2).

Discussion

The results of this phase 1, open-label study showed that the combination treatment of surufatinib and toripalimab was reasonably well-tolerated. Most TRAEs in this study were of low intensity (grade 1 or 2), and were manageable with dose adjustment or supportive medication. No treatment-related discontinuation or death was reported. The incidence of $\geq$ grade 3 TRAE or serious TRAE was comparable or slightly lower to data reported for surufatinib or toripalimab monotherapy [18–21], and was lower than those reported for other VEGF/VEGFR inhibitor plus PD-1 antibody combinations [15–16]. Compared with previously reported data from toripalimab and axitinib combination study, comparable incidence of immune-related AE was identified in our study [25].

There was no new safety signal noted in this study. Proteinuria, hypertension, and abnormal liver function are common in surufatinib monotherapy [18–19]; the frequencies of these adverse events in this study were consistent with previous findings. Common immune reactions related to toripalimab included hyperthyroidism, hypothyroidism, abnormal liver function, diabetes mellitus, and rash [20–21, 25]; the frequency of these events reported in this trial was comparable to those of previously reported results, with the exception of skin and subcutaneous tissue disorders (e.g. rash), which was clearly lower in our study. The findings in this study suggest that the combination of surufatinib with toripalimab does not cause overlapping toxicity.

It is noted that patients in 300 mg cohort experienced more $\geq$ grade 3 TRAEs. In addition, more treatment-related SAEs and immune-related AE were reported in the 300 mg cohort. According to these results, 200 mg or 250 mg surufatinib plus toripalimab are safer dosages.

PK analysis showed that surufatinib exposure ($AUC_{0-\tau}$) increased with the dose ascending from 200 to 300 mg on each sampling day. The toripalimab exposure ($AUC_{0-\tau}$) was similar on the same sampling day at different dose levels of concomitant surufatinib, which may indicate no obvious impact of surufatinib administration on the toripalimab exposure in patients.

We noted that among the 27 patients evaluable for efficacy, the majority of the patients with PR (5/6) were in 250 mg cohort, which was accompanied by the highest ORR (45.5%) and DCR (100%). In spite of the efficacy differences among the different dosage groups, which might due to multiple factors such as different tumor types and baseline characteristics, the efficacy results indicated that 250 mg QD surufatinib was the most effective dose in this combination therapy. Based on the observed promising preliminary efficacy results, as well as the favorable safety profile for 250 mg cohort, the RP2D was determined to be 250 mg QD surufatinib plus 240 mg Q3W toripalimab.

Of note, of the 18 NEN patients with evaluable tumor, the ORR and DCR was 22.2% and 83.3%, respectively. At the RP2D (250 mg cohort), the ORR and DCR was 50% and 100%, respectively, demonstrating the promising antitumor activity of this combination treatment in NENs patients. In a phase Ib/II trial of surufatinib in advanced well-differentiated NET, ORRs were 19% (95% CI 9–34) and 15% (95% CI 6–31) in the pancreatic and extrapancreatic NET cohorts, respectively, and DCRs were 91% (95% CI 77–97) and 92% (95% CI 79–98), respectively [18]. In our previous work of evaluating the safety and efficacy of using toripalimab in NEN patients ($Ki-67 \geq 10\%$) after failure of first line therapy, the ORR and DCR were 20% and 35%, respectively [26]. In this current study, the combination of surufatinib and toripalimab achieved a much higher response rate as well as DCR, compared with results from single agent studies, which indicates that there is a synergistic effect between these two agents. During preclinical phase, the mechanism of this combination was well studied. Tumor angiogenesis could be promoted by many factors, such as VEGF, basic fibroblast growth factor (bFGF), and platelet-derived endothelial growth factor (PDGF) [27]. Angiogenesis could induce an immunosuppressive tumor microenvironment and was found to be closely related with tumor immune escape [28]. The anti-VEGFR and FGFR treatment, such as surufatinib, could suppress tumor angiogenesis and overcome the resistance to VEGF/VEGFR inhibition, thus enhance the effect of immune check point inhibitors [23]. In addition to the inhibition of VEGFR and FGFR, surufatinib could also inhibit CSF-1R and CSF-1R is involved in tissue macrophage development and maintenance [29]. By inhibiting CSF-1R, surufatinib could significantly decrease CSF-1R positive M2 TAM infiltration in tumor tissues, and increase the infiltration of M1-TAM (iNOS+) and CD8 + T cell, which result in enhancement of immune response [23]. These findings indicate that surufatinib could simultaneously block tumor angiogenesis and modulate cancer immunity, which might explain the improved efficacy of the combination of surufatinib with toripalimab.

For the predictive biomarker exploration, we tested PD-L1 positive status in enrolled patients. In previous published results, the ORR of toripalimab and axitinib was higher in PD-L1 positive ($\geq 1\%$) patients [25], and PD-L1 expression seemed to be a good predictive marker for toripalimab [26]. However, in our study, we observed potential clinical benefit for the entire patient population, regardless of PD-L1 expression

(Supplementary Table S2). The ORR and DCR were comparable in PD-L1 positive and PD-L1 negative population. This might be due to the dual angio-immuno approach of surufatinib, by inhibiting a trifecta of cancer-promoting receptors [18–19]. Given the small sample size employed in our study, the potential for benefiting all patients regardless of PD-L1 expression requires confirmation in a larger randomized study.

Limitations

The limitations of this phase 1 study include the small sample size and the multiple types of tumors represented in the patient population. A phase 2 trial of surufatinib plus toripalimab (NCT04169672) has been initiated to further evaluate the efficacy and safety profile of this combination in advanced solid tumors, which mainly include NEN, biliary tract cancer, gastric cancer, thyroid cancer, small cell lung cancer, soft tissue sarcoma, endometrial carcinoma and esophageal squamous cell carcinoma.

Conclusions

In summary, surufatinib plus toripalimab was well tolerated with no unexpected safety signals observed and showed preliminary antitumor activity in patients with advanced solid tumor, particularly in NEN patients. This combination warrants further evaluations in clinical trials.

Abbreviations

ICIs: immune checkpoint inhibitors

PD-1: programmed death protein-1

PD-L1: programmed death ligand-1

MSI-H: microsatellite instability-high

dMMR: mismatch repair deficient

VEGF: vascular endothelial growth factor

VEGFR: vascular endothelial growth factor receptor

ORR: objective response rate

DCR: disease control rate

FGFR 1: fibroblast growth factor receptor 1

CSF-1R: colony stimulating factor 1 receptor

IgG4: immunoglobulin G4

TAMs: tumor-associated macrophages

ECOG PS: Eastern Cooperative Oncology Group performance status

RECIST: Response Evaluation Criteria in Solid Tumors

CNS: central nervous system

ICF: informed consent form

QD: once daily

Q3W: every 3 weeks

MTD: maximum tolerated dose

RP2D: recommended phase 2 dose

DLT: dose limited toxicity

PK: pharmacokinetic

PFS: progression-free survival

OS: overall survival

DoR: duration of response

TTR: time to response

AEs: adverse events

CTCAE: Common Terminology Criteria for Adverse Events

MedDRA: Medical Dictionary for Regulatory Activities

TRAEs: treatment-related AEs

C_{max}: maximum observed concentration

T_{max}: time to C_{max}

AUC_{0-τ}: area under the concentration-time curve for a dosing interval

NEN: neuroendocrine neoplasm

CRC: colorectal cancer

EC: esophageal squamous cell carcinoma

GC: gastric adenocarcinoma

NEC: neuroendocrine carcinoma

NET: neuroendocrine tumor

SAEs: serious adverse events

CR: complete response

PR: partial response

SD: stable disease

BOR: best overall response

bFGF: basic fibroblast growth factor

PDGF: platelet-derived endothelial growth factor

Declarations

Ethics approval and consent to participate

This clinical trial was approved by Ethics Committee of Peking University Cancer Hospital and was conducted strictly in accordance with the Declaration of Helsinki and Good Clinical Practice. All patients provided written informed consent form before enrollment.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on a reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author's contributions

ML, YC, LS were involved in study conception and design; ML, LS were involved in development of methodology; YC, ML, JG, Jie L, ZL, Jian L, XZ, YL, ZP, JZ, XW, LS contributed to acquisition of data; YC, ML, YS, JG, Jie L, ZL, Jian L, XZ, YL, ZP, JZ, XW, LS contributed to analysis and interpretation of data; YC, ML, LS contributed to writing, review, and revision of the manuscript; YC, ML, YS, JG, Jie L, ZL, Jian L, XZ, YL, ZP, JZ, XW were involved in administrative, technical, or material support; ML, LS contributed to study supervision; all authors read and approved the final manuscript.

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Tables

Table 1 Patient demographics and baseline characteristics (safety population)

	Surufatinib 200 mg QD + Toripalimab 240 mg Q3W (N=6) n (%)	Surufatinib 250 mg QD + Toripalimab 240 mg Q3W (N=12) n (%)	Surufatinib 300 mg QD + Toripalimab 240 mg Q3W (N=12) n (%)	Total (N=30) n (%)
Age (Years)				
Mean (standard deviation)	55.2±13.59	56.1±13.92	59.3±7.69	57.2 ±11.44
Median	57.0	61.5	61.5	61.0
Min, Max	36, 74	30, 71	45, 68	30, 74
Sex, n (%)				
Male	5 (83.3)	10 (83.3)	9 (75.0)	24 (80.0)
Female	1 (16.7)	2 (16.7)	3 (25.0)	6 (20.0)
Childbearing potential ^a				
Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No	1 (100.0)	2 (100.0)	3 (100.0)	6 (100.0)
Race, n(%)				
Asian	6 (100.0)	12 (100.0)	12 (100.0)	30 (100.0)
Non-Asian	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Height (cm)				
Mean (standard deviation)	169.50 ±8.216	167.50 ±10.553	168.63 ±6.050	168.35 ±8.268
Median	168.50	167.50	169.50	169.00
Min, Max	161.0, 180.0	147.0, 187.0	156.0, 175.0	147.0, 187.0

	Surufatinib 200 mg QD + Toripalimab 240 mg Q3W (N=6) n (%)	Surufatinib 250 mg QD + Toripalimab 240 mg Q3W (N=12) n (%)	Surufatinib 300 mg QD + Toripalimab 240 mg Q3W (N=12) n (%)	Total (N=30) n (%)
Weight (kg)				
Mean (standard deviation)	60.50 [15.202]	71.63 [16.205]	62.50 [10.002]	65.75 [14.204]
Median	59.00	69.75	60.50	61.75
Min, Max	40.0, 82.0	50.0, 98.0	49.0, 81.0	40.0, 98.0
BMI (kg/m²)				
Mean (standard deviation)	20.83 [3.816]	25.46 [4.998]	21.93 [2.918]	23.12 [4.375]
Median	20.70	24.50	21.60	22.30
Min, Max	15.4, 25.3	18.3, 36.9	16.3, 27.7	15.4, 36.9
Baseline ECOG PS, n (%)				
0	2 (33.3)	3 (25.0)	6 (50.0)	11 (36.7)
1	4 (66.7)	9 (75.0)	6 (50.0)	19 (63.3)
Cancer type, n (%)				
CRC	0 (0.0)	3 (25.0)	1 (8.3)	4 (13.3)
EC	0 (0.0)	1 (8.3)	1 (8.3)	2 (6.7)
GC	0 (0.0)	0 (0.0)	2 (16.7)	2 (6.7)
NEN	6 (100.0)	7 (58.3)	8 (66.7)	21 (70.0)
NEC	3 (50.0)	5 (41.7)	5 (41.7)	13 (43.3)
NET G2	0 (0.0)	1 (8.3)	3 (25.0)	4 (13.3)

	Surufatinib 200 mg QD + Toripalimab 240 mg Q3W (N=6) n (%)	Surufatinib 250 mg QD + Toripalimab 240 mg Q3W (N=12) n (%)	Surufatinib 300 mg QD + Toripalimab 240 mg Q3W (N=12) n (%)	Total (N=30) n (%)
NET G3	3 (50.0)	1 (8.3)	0 (0.0)	4 (13.3)
Metastatic squamous cell carcinoma	0 (0.0)	1 (8.3)	0 (0.0)	1 (3.3)
Site of primary tumor¹, n (%)				
Colon	0 (0.0)	0 (0.0)	1 (8.3)	1 (3.3)
Esophagus	0 (0.0)	0 (0.0)	1 (8.3)	1 (3.3)
Stomach/Gastroesophageal junction	2 (33.3)	3 (25)	1 (8.3)	6 (20)
Lung	0 (0.0)	1 (8.3)	0 (0.0)	1 (3.3)
Pancreas	2 (33.3)	1 (8.3)	1 (8.3)	4 (13.3)
Rectum	2 (33.3)	0 (0.0)	2 (16.7)	4 (13.3)
Other	0 (0.0)	1 (8.3)	2 (16.7)	3 (10.0)
Time from initial diagnosis to first dose of study drug(months)				
Mean (standard deviation)	17.17 [5.819]	16.88 [8.253]	24.69 [20.607]	20.06 [14.406]
Median	16.89	16.39	21.72	18.28
Min, Max	11.4, 26.5	4.9, 37.2	3.0, 70.4	3.0, 70.4
Tumor stage at screening, n (%)				
I	6 (100.0)	12 (100.0)	12(100)	30 (100)

BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; PS, performance status; CRC, colorectal cancer; EC, esophageal squamous cell carcinoma; GC, gastric cancer; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor.

¹Site of primary tumor was only collected for patients with NEC.

Table 2 Summary of treatment-related AEs (safety population)*

	Surufatinib 200 mg QD + Toripalimab 240 mg Q3W (N=6) n(%)		Surufatinib 250 mg QD + Toripalimab 240 mg Q3W (N=12) n(%)		Surufatinib 300 mg QD + Toripalimab 240 mg Q3W (N=12) n(%)		Total (N=30) n(%)	
Preferred Term	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Subjects with any treatment-related AE	6 (100.0)	1 (16.7)	12 (100.0)	4 (33.3)	12 (100.0)	9 (75.0)	30 (100.0)	14 (46.7)
Proteinuria ¹	6 (100.0)	0 (0.0)	9 (75.0)	0 (0.0)	11 (91.7)	0 (0.0)	26 (86.7)	0 (0.0)
Fecal occult blood positive ²	5 (83.3)	0 (0.0)	8 (66.7)	0 (0.0)	10 (83.3)	0 (0.0)	23 (76.7)	0 (0.0)
Blood bilirubin increased ³	5 (83.3)	0 (0.0)	8 (66.7)	0 (0.0)	9 (75.0)	3 (25.0)	22 (73.3)	3 (10.0)
Hypothyroidism	3 (50.0)	0 (0.0)	6 (50.0)	0 (0.0)	11 (91.7)	0 (0.0)	20 (66.7)	0 (0.0)
Hypertension ⁴	5 (83.3)	0 (0.0)	3 (25.0)	2 (16.7)	8 (66.7)	2 (16.7)	16 (53.3)	4 (13.3)
Blood urine present ⁵	1 (16.7)	0 (0.0)	7 (58.3)	0 (0.0)	8 (66.7)	0 (0.0)	16 (53.3)	0 (0.0)
Transaminases increased ⁶	3 (50.0)	1 (16.7)	3 (25.0)	0 (0.0)	7 (58.3)	4 (33.3)	13 (43.3)	5 (16.7)
White blood cell count decreased	4 (66.7)	0 (0.0)	3 (25.0)	0 (0.0)	6 (50.0)	0 (0.0)	13 (43.3)	0 (0.0)
Anaemia ⁷	0 (0.0)	0 (0.0)	3 (25.0)	1 (8.3)	8 (66.7)	1 (8.3)	11 (36.7)	1 (6.7)
Hyperthyroidism	2 (33.3)	0 (0.0)	1 (8.3)	0 (0.0)	4 (33.3)	1 (8.3)	7 (23.3)	1 (3.3)
Amylase increased	2 (33.3)	0 (0.0)	4 (33.3)	0 (0.0)	2 (16.7)	1 (8.3)	8 (26.7)	1 (3.3)
Blood urea increased	0 (0.0)	0 (0.0)	4 (33.3)	0 (0.0)	3 (25.0)	0 (0.0)	7 (23.3)	0 (0.0)
Neutrophil count decreased	2 (33.3)	0 (0.0)	1 (8.3)	0 (0.0)	4 (33.3)	0 (0.0)	7 (23.3)	0 (0.0)
Blood creatine phosphokinase increased	1 (16.7)	0 (0.0)	1 (8.3)	0 (0.0)	4 (33.3)	1 (8.3)	6 (20.0)	1 (3.3)

	Surufatinib 200 mg QD + Toripalimab 240 mg Q3W (N=6) n(%)		Surufatinib 250 mg QD + Toripalimab 240 mg Q3W (N=12) n(%)		Surufatinib 300 mg QD + Toripalimab 240 mg Q3W (N=12) n(%)		Total (N=30) n(%)	
Preferred Term	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Blood creatine phosphokinase MB increased	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)	5 (41.7)	0 (0.0)	6 (20.0)	0 (0.0)
Vomiting	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)	3 (25.0)	2 (16.7)	4 (13.3)	2 (6.7)
Asthenia	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (16.7)	2 (16.7)	3 (10.0)	2 (6.7)

*Treatment-related AEs of any grade occurring in ≥20% of total patients or treatment-related grade 3 or worse AEs occurring in ≥5% of total patients (safety population).

AE, adverse event.

¹Proteinuria included proteinuria and protein urine present.

²Fecal occult blood positive included fecal occult blood positive, occult blood positive and occult blood.

³Blood bilirubin increased included blood bilirubin increased, total bilirubin increased, direct bilirubin increased, indirect bilirubin increased and bilirubin increased.

⁴Hypertension included hypertension and blood pressure increased.

⁵Blood urine present included blood urine present and red blood cells urine positive.

⁶Transaminases increased included transaminases increased, alanine aminotransferase increased and aspartate aminotransferase increased.

⁷Anaemia included anaemia and haemoglobin decreased.

Table 3 PK parameters of surufatinib and toripalimab (PK population)

Surufatinib							
Dose (mg)		Day	N	C _{max} (ng/mL)	T _{max} (h)		AUC _{0-τ} (h×ng/mL)
Surufatinib	Toripalimab			Geometric mean (CV%)	Median	min, max	Geometric mean (CV%)
200	240	C1D1	6	277 (27.9)	1.98	1.08, 4.00	1845 (8.53)
250	240	C1D1	12	289 (58.3)	1.58	1.00, 4.00	1845 (54.3)
300	240	C1D1	12	228 (46.3)	2.00	1.10, 4.00	1878 (72.4)
200	240	C2D1	6	268 (55.0)	2.97	1.90, 4.00	3013 (42.6)
250	240	C2D1	11	407 (71.4)	2.00	1.00, 4.03	3610 (68.0)
300	240	C2D1	10	281 (34.0)	2.97	1.00, 7.93	3668 (30.4)
200	240	C3D1	3	239 (53.6)	1.98	1.98, 4.00	2298 (24.3)
250	240	C3D1	9	310 (58.8)	1.93	1.00, 4.00	2398 (52.3) ¹
300	240	C3D1	10	361 (31.7)	2.00	1.90, 4.10	3496 (30.1)
Toripalimab							
Dose (mg)		Day	N	C _{max} (μg/mL)	T _{max} (h)		AUC _{0-τ} (h×μg/mL)
Surufatinib	Toripalimab			Geometric mean (CV%)	Median	min, max	Geometric mean (CV%)
200	240	C1D1	6	78.1 (15.2)	1.96	0.78, 6.63	15925 (22.8)
250	240	C1D1	12	71.4 (21.6)	1.85	1.03, 24.4	14142 (25.6)
300	240	C1D1	12	81.2 (24.5)	1.12	0.70, 6.78	16458 (25.0)
200	240	C2D1	4	96.2 (17.9)	2.63	1.32, 6.63	21512 (26.4)
250	240	C2D1	11	83.8 (24.5)	1.13	0.62, 6.68	17176 (31.5)

300	240	C2D1	10	98.1 (27.5)	1.26	0.63, 24.2	20660 (33.7)
200	240	C3D1	3	110 (29.0)	1.45	0.98, 2.72	24626 (34.9)
250	240	C3D1	10	97.4 (25.0)	1.87	0.58, 24.2	20157 (39.5)
300	240	C3D1	9	103 (33.2)	1.17	0.72, 24.2	20063 (46.6)

C: Cycle; D: Day; PK, pharmacokinetics; $C_{\max}$, maximum observed concentration; $T_{\max}$, time to $C_{\max}$; $AUC_{0-\tau}$, area under the concentration-time curve for a dosing interval; CV, coefficient of variation.

¹N for $AUC_{0-\tau}$ in C3D1 was eight.

Table 4 Tumor response of surufatinib plus toripalimab (efficacy evaluable population)

	Surufatinib 200 mg QD + Toripalimab 240 mg Q3W (N=6) n (%)	Surufatinib 250 mg QD + Toripalimab 240 mg Q3W (N=11) n (%)	Surufatinib 300 mg QD + Toripalimab 240 mg Q3W (N=12) n (%)	Total (N=29) n (%)
Confirmed best overall response (based on RECIST v1.1)				
CR	1 (16.7)	0 (0.0)	0 (0.0)	1 (3.4)
PR	0 (0.0)	5 (45.5)	1 (8.3)	6 (20.7)
SD	2 (33.3)	6 (54.5)	8 (66.7)	16 (55.2)
PD	3 (50.0)	0 (0.0)	3 (25.0)	6 (20.7)
ORR¹	1 (16.7)	5 (45.5)	1 (8.3)	7 (24.1)
95% CI of ORR	0.4–64.1	16.7–76.6	0.2–38.5	10.3–43.5
DCR²	3 (50.0)	11 (100.0)	9 (75.0)	23 (79.3)
95% CI of DCR	11.8–88.2	71.5–100.0	42.8–94.5	60.3–92.0

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate. CI, confidential interval; RECIST, Response Evaluation Criteria in Solid Tumors.

¹ORR was defined as the proportion of patients with confirmed best overall response of CR or PR.

²DCR was defined as the proportion of patients with best overall response of CR or PR or SD.

Figures

Figure 1

Figure 1

(A) Waterfall Plot – Best Percent Change from Baseline in Sum of Target Lesion Diameters (Efficacy Evaluable Population) *; (B) Spider Plot – Percent Change from Baseline in Sum of Target Lesion Diameters Over Time (Efficacy Evaluable Population) *; (C) Swimmer Plot – Response Pattern of Each Subject (Efficacy Evaluable Population). *Only assessments prior to initial of a new anti-cancer therapy

included in the analysis. Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Figure 1

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(A) Waterfall Plot – Best Percent Change from Baseline in Sum of Target Lesion Diameters (Efficacy Evaluable Population) *; (B) Spider Plot – Percent Change from Baseline in Sum of Target Lesion Diameters Over Time (Efficacy Evaluable Population) *; (C) Swimmer Plot – Response Pattern of Each

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(A) Waterfall Plot – Best Percent Change from Baseline in Sum of Target Lesion Diameters (Efficacy Evaluable Population) *; (B) Spider Plot – Percent Change from Baseline in Sum of Target Lesion

Diameters Over Time (Efficacy Evaluable Population) *; (C) Swimmer Plot – Response Pattern of Each Subject (Efficacy Evaluable Population). *Only assessments prior to initial of a new anti-cancer therapy included in the analysis. Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Supplementary Files

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