A phase Ib/II trial of capmatinib plus spartalizumab *vs.* spartalizumab alone in patients with pretreated hepatocellular carcinoma

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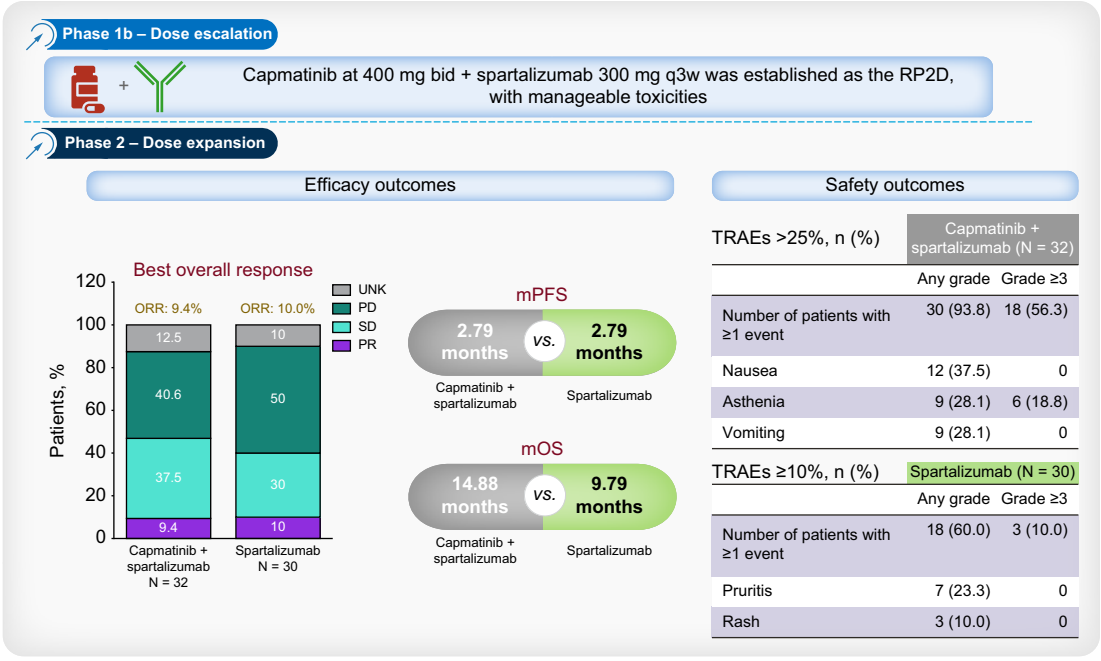
Graphical abstract



Highlights

- First trial reporting on the combination of a MET and a PD-1 inhibitor as a second-line treatment after sorafenib for advanced HCC.
- The RP2D for capmatinib in combination with spartalizumab at 300 mg q3w was set at 400 mg bid.
- Preliminary clinical activity of capmatinib in combination with spartalizumab was observed during a phase Ib study.
- However, the combination did not show superior clinical activity compared to spartalizumab alone in phase II.
- No new safety concerns were raised and toxicities were manageable in this study.

Impact and implications

Simultaneous targeting of MET and programmed cell death protein 1 may provide synergistic clinical benefit in patients with advanced HCC. This is the first trial to report a combination of capmatinib (MET inhibitor) and spartalizumab (programmed cell death protein 1 inhibitor) as second-line treatment after sorafenib for advanced HCC. The combination did not show superior clinical activity compared with spartalizumab single-agent treatment in patients with advanced HCC who had previously been treated with sorafenib. The results indicate that there is a clear need to identify a reliable predictive marker of response for HCC and to identify patients with HCC that would benefit from the combination of checkpoint inhibitor +/- targeted therapy.

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Research article

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A phase Ib/II trial of capmatinib plus spartalizumab *vs.* spartalizumab alone in patients with pretreated hepatocellular carcinoma

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Background & aims: This phase Ib/II trial evaluated the safety and efficacy of capmatinib in combination with spartalizumab or spartalizumab alone in patients with advanced hepatocellular carcinoma (HCC).
Methods: Eligible patients who had progressed or were intolerant to sorafenib received escalating doses of capmatinib 200 mg, 300 mg, and 400 mg twice a day (bid) plus spartalizumab 300 mg every 3 weeks (q3w) in the phase Ib study. Once the recommended phase II dose (RP2D) was determined, the phase II study commenced with randomised 1:1 treatment with either capmatinib + spartalizumab (n = 32) or spartalizumab alone (n = 30). Primary endpoints were safety and tolerability (phase Ib) and investigator-assessed overall response rate per RECIST v1.1 for combination *vs.* single-agent arms using a Bayesian logistic regression model (phase II).
Results: In phase Ib, the RP2D for capmatinib in combination with spartalizumab was determined to be 400 mg bid. Dose-limiting toxicity consisting of grade 3 diarrhoea was reported in one patient at the capmatinib 400 mg bid + spartalizumab 300 mg q3w dose level. The primary endpoint in the phase II study was not met. The observed overall response rate in the capmatinib + spartalizumab arm was 9.4% *vs.* 10% in the spartalizumab arm. The most common any-grade treatment-related adverse events (TRAEs, ≥20%) were nausea (37.5%), asthenia and vomiting (28.1% each), diarrhoea, pyrexia, and decreased appetite (25.0% each) in the combination arm; TRAEs ≥10% were pruritus (23.3%), and rash (10.0%) in the spartalizumab-alone arm.
Conclusion: Capmatinib at 400 mg bid plus spartalizumab 300 mg q3w was established as the RP2D, with manageable toxicities and no significant safety signals, but the combination did not show superior clinical activity compared with spartalizumab single-agent treatment in patients with advanced HCC who had previously been treated with sorafenib.
Impact and implications: Simultaneous targeting of MET and programmed cell death protein 1 may provide synergistic clinical benefit in patients with advanced HCC. This is the first trial to report a combination of capmatinib (MET inhibitor) and spartalizumab (programmed cell death protein 1 inhibitor) as second-line treatment after sorafenib for advanced HCC. The combination did not show superior clinical activity compared with spartalizumab single-agent treatment in patients with advanced HCC who had previously been treated with sorafenib. The results indicate that there is a clear need to identify a reliable predictive marker of response for HCC and to identify patients with HCC that would benefit from the combination of checkpoint inhibitor +/- targeted therapy.
Clinical trial number: NCT02795429.

Keywords: Capmatinib; Spartalizumab; Hepatocellular carcinoma; MET; anti-programmed death-ligand 1.
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Introduction

Hepatocellular carcinoma (HCC) accounts for approximately 75–85% of liver cancer cases worldwide and is the third leading cause of cancer-related mortality globally.[1] Most patients require systemic therapy as a result of advanced or metastatic disease at diagnosis or disease recurrence after local interventions with curative intent.[2,3]

Sorafenib was the first approved targeted therapy for advanced HCC.[4] Since 2020, multikinase inhibitors (MKIs), including regorafenib, cabozantinib, and the monoclonal antibody ramucirumab, have been approved for patients who had progressed on sorafenib. Pivotal phase 3 trials have reported median overall survival (OS) ranging from 8.5 to 13.6 months.[5–7] More recently, a combination of atezolizumab (anti-programmed death ligand 1 (PD-L1) antibody) and bevacizumab (anti-vascular endothelial growth factor A antibody) has been approved as first-line (1L) therapy and is considered as standard of care in patients with advanced HCC, based on its superiority over sorafenib in the pivotal IMbrave150 trial.[8]

Despite the availability of novel therapies, the overall prognosis for advanced HCC is poor,[9] and data to guide the optimal choice of therapy after progression on immunotherapy or after progression on 1L MKI are still limited.[10]

MET aberrations are oncogenic drivers in HCC and have been associated with resistance to sorafenib and lenvantinib therapy in HCC.[9] Furthermore, autocrine or paracrine activation of MET by HGF was found to drive the growth and migration of HCC cell lines *in vitro*.[11] Paracrine stimulation of cancer cells by HGF originating from non-cancerous liver tissue has also been known to promote tumour growth and metastasis, independent of the dysregulation of the MET pathway.[12] MET inhibition abrogates the growth of MET-activated HCC cells by blocking MET phosphorylation and activation of downstream PI3K and MAPK pathways.[13]

Capmatinib is a highly potent and selective type Ib MET inhibitor (METi) that blocks MET phosphorylation by competing with ATP for the ATP-binding pocket of the active conformation of MET, thus preventing abnormal activation of downstream signalling pathways in tumour cells.[14,15] Capmatinib has shown antitumor activity in preclinical HCC models that are driven either by amplification of the *MET* gene or by HGF stimulation.[16] Preliminary antitumor activity of capmatinib was also observed in a subset of patients with MET-high expressing HCC.[17]

The presence of tumour-infiltrating lymphocytes expressing PD-1 in HCC lesions and their correlation with outcome suggests that immune checkpoint inhibitors (ICIs) could be useful in this setting.[18,19] Spartalizumab, a humanised immunoglobulin G4 monoclonal antibody targets PD-1, preventing its binding to programmed death-ligand 1 (PD-L1) and PD-L2, thus restoring effector T-cell function, leading to T-cell proliferation, cytokine production, and cytolytic function, ultimately improving antitumor response. Spartalizumab has demonstrated a favourable safety profile and signs of antitumor activity in patients with advanced solid tumors.[20]

Clinical activity of METi and PD-1 inhibitors as monotherapy in advanced HCC has previously been reported.[21–24] The positive outcomes from early clinical trials of putative METi tivantinib[21] and tepotinib[22] in the treatment of HCC supported the evaluation of MET targeted agents in HCC. Single-agent PD-1 inhibition by nivolumab (CheckMate 040[23]) and pembrolizumab (KEYNOTE-224[24]) demonstrated promising activity in early clinical trials. Interestingly, inhibition of MET by pharmacological or genetic means can enhance the antitumor response mediated by T cells when combined with anti-PD-1 agents in a variety of *in vivo* mouse models, regardless of the MET status of the tumour.[25] Consistent with these reports, our unpublished preclinical findings using two syngeneic mouse models also demonstrated that combination treatment of spartalizumab with capmatinib led to higher T cell infiltration and improved antitumor immune response than that observed to single-agent spartalizumab. Collectively, this evidence provides strong support for the evaluation of a METi capmatinib in combination with an anti-PD-1 spartalizumab to enhance antitumor activity in advanced HCC.

The purpose of this phase Ib/II study was to determine the safety and recommended phase II dose (RP2D) of the capmatinib plus spartalizumab combination (phase Ib), and to further assess the safety and clinical activity of capmatinib in combination with spartalizumab and spartalizumab as a single agent in patients with advanced HCC who had progressed on sorafenib or were intolerant to sorafenib treatment (phase II).

Patients and methods

Study design

This was an open-label, randomised, multicentre phase Ib/II trial conducted in 18 centres world-wide, including China, the Republic of Korea, Hong Kong, France, Taiwan, Germany, Italy, and Canada. The study was conducted in two parts, with the phases conducted sequentially. The phase Ib dose-escalation part was designed to establish the RP2D of capmatinib plus spartalizumab. This was followed by a phase II study to assess the safety and efficacy of capmatinib in combination with spartalizumab or of spartalizumab as a single agent (Fig. 1). The patients from phase Ib of the study could not roll over into the phase II study.

The study protocol was reviewed and approved by the institutional review boards of each participating institution, and the study was conducted in accordance with the principles of the Declaration of Helsinki. All patients provided their informed consent in writing prior to screening.

Patients and methods

This study included adult patients (aged ≥18 years) with histologically or cytologically documented locally advanced, recurrent, or metastatic HCC. Patients required ≥1 measurable lesion per Response Evaluation Criteria in Solid Tumours (RECIST) v.1.1[26] and Eastern Cooperative Oncology Group performance status (ECOG PS) ≤1. Enrolment was restricted to patients with prior sorafenib treatment for HCC with documented progression during or after discontinuation of sorafenib or those were intolerant to sorafenib; Child-Pugh Class A[27] with no encephalopathy and/or clinically significant ascites; and no previous systemic anticancer therapies other than sorafenib and no concomitant treatment with chronic steroid therapy or immunosuppressive therapy (≥10 mg/day prednisone or equivalent). Patients who were not candidates for locoregional treatment (*e.g.,* hepatic resection, hepatic arterial embolisation), had no history of interstitial lung disease/pneumonitis, and no symptomatic central nervous system (CNS) metastases or CNS metastases requiring therapy were eligible for inclusion. Prior treatment with sorafenib was a key inclusion criterion, however, disease progression on sorafenib was not mandated. Patients who were intolerant to sorafenib (defined, per protocol, as documented grade 3/4 adverse event [AE] leading to discontinuation of sorafenib treatment) were also eligible for this study.

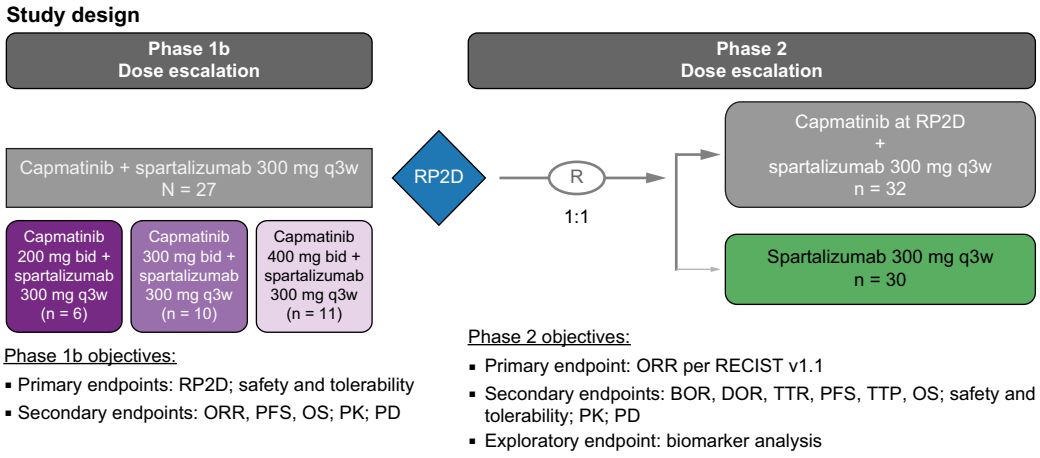

Fig. 1. Study design. bid, twice daily; BOR, best overall response; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PD, pharmacodynamics; PK, pharmacokinetics; q3w, once in every 3 weeks; R, randomisation; RECIST, Response Evaluation Criteria in Solid Tumours; RP2D, recommended phase II dose; TTR, time to response; TTP, time to progression.

Treatment

During the phase Ib part of the study, 27 patients were treated with capmatinib in combination with a fixed dose of spartalizumab until the RP2D was established. The capmatinib tablet was administered orally twice daily (bid) on a continuous dosing schedule, on a flat scale of mg/day, and was not adjusted individually by weight or body surface area. The doses administered in phase Ib were 200 mg bid (starting dose; n = 6), 300 mg bid (n = 10), and 400 mg bid (n = 11). Spartalizumab 300 mg (powder for solution for infusion) was administered intravenously for 30 min (up to 2 h, if clinically indicated) once every 3 weeks (q3w) (Fig. 1). The dose escalation was guided by a Bayesian logistic regression model (BLRM) following the escalation with overdose control (EWOC) principle. A complete cycle of treatment was defined as 21 days for study treatment and the dose-limiting toxicity (DLT) period as two cycles.

Once RP2D was declared, additional patients were enrolled in the phase II part to assess the antitumor activity of capmatinib in combination with spartalizumab *vs.* spartalizumab single agent. A total of 62 patients were randomly assigned in a 1:1 ratio to capmatinib treatment in combination with spartalizumab (n = 32) or spartalizumab single agent (n = 30; Fig. 1). Capmatinib 400 mg bid plus spartalizumab 300 mg q3w were administered until the appearance of unacceptable toxicity, progressive disease according to immune-related response criteria (irRC), and/or treatment was discontinued at the discretion of the investigator or patient.

Study endpoints

The primary endpoints included the incidence and severity of AEs, serious AEs (SAEs), and DLTs (phase Ib); and investigator-assessed overall response rate (ORR) per RECIST v1.1 (phase II). Secondary endpoints in phases 1b/2 included the best overall response (BOR), duration of response (DOR), time to response (TTR), progression-free survival (PFS), time to progression (TTP) by investigator evaluation according to RECIST v1.1 and by irRC, OS, safety and tolerability (phase II), pharmacokinetics (PK) and pharmacodynamics (PD). The exploratory endpoints included biomarker analysis.

Statistical analysis

Analysis of primary endpoints

In phase Ib, the estimation of RP2D of the treatment was based on the estimation of the probability of DLT in cycles 1 and 2 for patients in the dose-determining analysis set. Dose escalation was guided by a BLRM of DLT data in cycles 1 and 2 for capmatinib and spartalizumab. The Bayesian analysis was based on a model with three parts, representing single-agent capmatinib toxicity, single-agent spartalizumab toxicity, and their interaction. Single-agent toxicity was modelled using logistic regression for the probability of a patient experiencing a DLT against log-dose. The odds of a DLT were then calculated under no interaction for the two single agent toxicities, and the interaction was taken into account by adjusting these odds with an additional model parameter (odds multiplier). After each treatment group of patients, the posterior distribution for the risk of DLT for new patients at combination doses of interest was evaluated. Dosing decisions also took into consideration the EWOC principle, according to which a combination dose could only be used for newly enrolled patients if the risk of excessive toxicity at that combination dose was less than 25%.

Estimation of the true ORR in the phase II part of the study was based on the observed overall response for patients in the full analysis set, using Bayesian analysis. The primary efficacy endpoint ORR was determined according to RECIST v1.1 for the primary analysis. A Bayesian logistic regression model with treatment (combination *vs.* single agent) was applied to provide the inference of ORR for the primary analysis. ORRs of the arms capmatinib plus spartalizumab and spartalizumab were compared. According to the study protocol, if the posterior probability of odds ratio (ORR [capmatinib + spartalizumab] to ORR [spartalizumab]) >1 was greater than 0.8 and the observed ORR (capmatinib + spartalizumab) was at least 10% greater than the observed ORR (spartalizumab), it could be concluded that the combination treatment has a superior antitumour effect compared with the spartalizumab single-agent treatment. The posterior mean of ORR adjusted for stratification factor was

provided, along with a 95% credible interval, and the probabilities that the true ORR lies in the following efficacy categories were reported: [0, 20%)–no antitumor activity and [20%, 100%)–clinically relevant antitumor activity.

Study assessments and other details regarding statistical analyses are described in the Supplementary Methods.

Results

Study enrolment took place from 15 June 2016, to 24 June 2021, with a median follow-up of 164 days (range: 28–1181 days).

Phase Ib

Patient characteristics and disposition

All 27 patients treated across the three dose levels discontinued the study treatment. The primary reason for discontinuation of study treatment was progressive disease (50.0% in the capmatinib 200 mg + spartalizumab 300 mg arm, 70.0% in the capmatinib 300 mg + spartalizumab 300 mg arm, and 54.5% in the capmatinib 400 mg + spartalizumab 300 mg arm). Of 27 patients, 19 (70.4%) had prior disease progression on sorafenib, and eight patients (29.6%) discontinued prior sorafenib treatment because of toxicity.

The baseline demographics and clinical characteristics are summarised in Table S1. The median age was 67.0 years (range: 45–78 years); the majority were male (85.2%) and Caucasian (59.3%), with an ECOG PS of 0/1 in 55.6/44.4% at baseline. In general, a lower proportion of patients were positive for HBV (25.9%) and HCV (3.7%). About 22.2% and 51.9% of the patients had received prior radiotherapy and prior antineoplastic surgery, respectively.

Efficacy

The efficacy-related outcomes of the phase Ib study are presented in Table 1. In the overall group (N = 27), the ORR and DCR assessed by the investigator per RECIST v1.1 were 14.8% (n = 4, 95% CI: 4.2–33.7) and 51.9% (n = 14, 95% CI: 31.9–71.3), respectively. The best percentage changes from baseline in the sum of the longest lesion diameters are shown in Fig. 2A. Overall, the median PFS was 3.35 months (n = 22, 95% CI: 1.4–5.6), median TTP was 3.35 months (n = 21, 95% CI: 1.4–5.6), and the median OS was 13.73 months (n = 22, 95% CI: 7.4–20.6), respectively. The median DOR and TTR were not estimable because of the low number of responders in phase Ib (fewer than 10 patients achieved a confirmed complete response (CR) or partial response (PR) in any treatment arm). The efficacy results of irRC were generally consistent with the results reported by RECIST v1.1 and are presented in the Supplementary Results.

Safety and tolerability

The overall median duration of exposure for all patients was 27.0 weeks (range: 3–166 weeks). Based on considerations of the recommendation of the BLRM and the general assessment of safety and PK data, the RP2D of the combination of capmatinib and spartalizumab was determined as a capmatinib 400 mg bid with spartalizumab 300 mg q3w. A DLT was reported in 1 patient (11.1%) at the capmatinib 400 mg + spartalizumab 300 mg dose level. The reported DLT was grade 3 diarrhoea, considered related to study treatment. The event led to permanent discontinuation of study treatment, was managed with concomitant medications, and resolved in 2 days.

Overall, 26 patients (96.3%) had at least one AE, any grade, regardless of the relationship with study treatment (Table S2). The most frequently reported AEs (>30%, any grade, regardless of relationship to study treatment) were peripheral oedema (59.3%), increased alanine transaminase (ALT) (37.0%), fatigue, nausea, and pruritus (33.3% each). Grade ≥3 (≥10%) AEs were increased ALT, increased aspartate aminotransferase (AST), and increased blood bilirubin (14.8% each).

Overall, 81.5% of the patients had at least one AE, of any grade, suspected to be related to the study treatment. Treatment-related AEs (TRAEs; ≥20%, any grade) were reported to be peripheral oedema (51.9%), increased ALT (29.6%), increased AST, fatigue, and pruritus (25.9% each), and increased blood creatinine, nausea, and rash (22.2% each).

In total, eight patients (29.6%) had at least one SAE (any grade, regardless of relationship to study treatment); SAEs suspected to be related to the study treatment were reported in five patients (45.5%) in the capmatinib 400 mg bid + spartalizumab 300 mg q3w dose level. No SAEs suspected to be treatment related were reported in the other two dose levels.

A total of five deaths (18.5%) occurred during the on-treatment period (*i.e.*, while on treatment or within 30 days after study treatment discontinuation). Four deaths (14.8%) were

Table 1. Investigator-assessed BOR, PFS, and OS per RECIST v1.1 across capmatinib dose levels: Phase Ib (FAS).

Efficacy parameter	Capmatinib 200 mg + spartalizumab 300 mg n = 6	Capmatinib 300 mg + spartalizumab 300 mg n = 10	Capmatinib 400 mg + spartalizumab 300 mg n = 11	All patients N = 27
BOR, n (%)				
CR	0	0	0	0
PR	2 (33.3)	0	2 (18.2)	4 (14.8)
SD	1 (16.7)	7 (70.0)	2 (18.2)	10 (37.0)
PD	3 (50.0)	2 (20.0)	7 (63.6)	12 (44.4)
Unknown	0	1 (10.0)	0	1 (3.7)
ORR (CR + PR), n (%) [95% CI]	2 (33.3) [4.3–77.7]	0 [0.0–30.8]	2 (18.2) [2.3–51.8]	4 (14.8) [4.2–33.7]
DCR (CR + PR + SD), n (%) [95% CI]	3 (50.0) [11.8–88.2]	7 (70.0) [34.8–93.3]	4 (36.4) [10.9–69.2]	14 (51.9) [31.9–71.3]
PFS				
Events, n (%)	5 (83.3)	8 (80.0)	9 (81.8)	22 (81.5)
Median (95% CI), months	3.42 (1.18–NA)	4.44 (1.25–NA)	1.35 (1.22–13.73)	3.35 (1.35–5.65)
OS				
Events, n (%)	6 (100)	8 (80.0)	8 (72.7)	22 (81.5)
Median (95% CI), months	14.98 (2.37–NA)	12.11 (1.68–19.45)	16.53 (2.83–NA)	13.73 (7.36–20.63)

BOR, best overall response; CR, complete response; DCR, disease control rate; FAS, full analysis set; NA, not achieved; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; SD, stable disease.

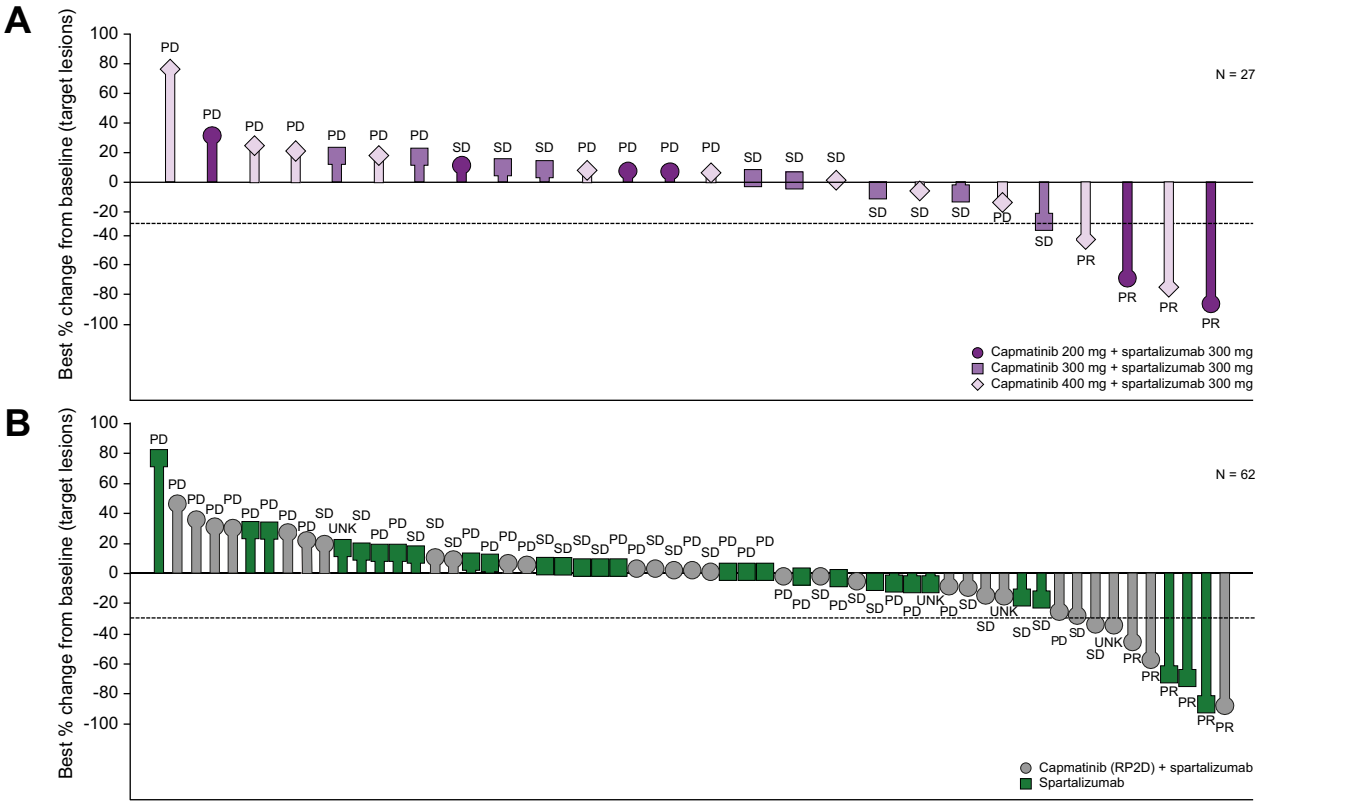

Fig. 2. Waterfall plots for best percentage change from baseline in target lesion per RECIST 1.1. (A) Phase Ib dose levels (FAS) and (B) Phase II (FAS). n = number of subjects with a baseline and at least 1 post-baseline assessment of target lesions based on investigator's assessment. *Percentage changes from baseline >100% are set to 100%. FAS, full analysis set; PD, pharmacodynamics; RECIST, response evaluation criteria in solid tumours; RP2D, recommended phase II dose; SD, standard deviation; UNK, unknown.

because of disease progression and one patient in the capmatinib 400 mg bid + spartalizumab 300 mg q3w dose level died because of cardiac arrest, considered to be related to study treatment. Further details regarding safety data are provided in the Supplementary Results.

Phase II

Patient characteristics and disposition

All 62 patients enrolled in phase II discontinued the study treatment, mainly because of progressive disease (81.3% in the combination arm and 66.7% in the spartalizumab-alone arm), as shown in Fig. S1. Of these 62 patients, 43 (69.4%) had prior disease progression to sorafenib, and 19 patients (30.6%) discontinued prior sorafenib treatment because of toxicity.

The baseline demographic and clinical characteristics were well balanced between the treatment arms (Table 2). Overall, the median age of patients in phase II was 65.0 years (range: 34–85 years); the majority were male (87.1%), had an ECOG PS of 0 (66.1%). The proportion of patients positive for HBV (33.9%) and HCV (22.6%) was considerably low.

Efficacy

The study's primary efficacy endpoint of ORR per RECIST v1.1 was not met in the phase II study. The posterior probability of odds ratio (ORR [capmatinib + spartalizumab] to ORR [spartalizumab]) ≥1 was 0.56, which did not meet the predefined criteria of >0.8, and the observed ORR of the combination treatment was not >10% greater than the observed ORR of spartalizumab single-agent treatment (9.4% *vs.* 10.0% as per investigator based on RECIST 1.1, respectively, and 12.5% *vs.* 10.0% as per investigator assessment based on irRC, respectively).

The secondary efficacy endpoints (including BOR, DCR, PFS, and OS) are presented in Table 3. The DCR was 46.9% (n = 15, 95% CI: 29.1–65.3) and 40.0% (n = 12, 95% CI: 22.7–59.4) in the combination and spartalizumab-alone arms, respectively. The best percentage changes from baseline in the sum of the longest lesion diameters in both arms are shown in Fig. 2B. At the time of the PFS analysis, 56 (90.3%) events had occurred in total (n = 30 for the combination arm, n = 26 for the spartalizumab-alone arm). The median PFS (95% CI) was 2.79 months (2.6–3.9) and 2.79 months (1.4–4.1) in the combination and the spartalizumab-alone arms, respectively (Fig. 3A). The median TTP was 2.79 months (n = 30, 95% CI: 2.6–3.9) in the combination arm and 2.79 months (n = 26, 95% CI:1.4–4.1) in the spartalizumab-alone arm. The median OS was 14.88 months (n = 23, 95% CI: 9.0–19.5) and 9.79 (n = 22, 95% CI: 3.6–22.3) for the combination and spartalizumab-alone arms, respectively (Fig. 3B). The DOR and TTR were not estimable because of the low number of responders (fewer than 10 patients achieved a confirmed CR or PR in each treatment arm). The efficacy results by irRC were generally consistent with the outcomes reported by RECIST v1.1 and are presented in the Supplementary Results.

Table 2. Demographics and disease characteristics: Phase II (FAS).

Demographic variable	Capmatinib (RP2D) + spartalizumab n = 32	Spartalizumab n = 30	All patients N = 62
Age, years, median (min–max)	65.5 (34–85)	64.5 (40–78)	65.0 (34–85)
Age category, n (%)			
18 to <65 years	15 (46.9)	15 (50.0)	30 (48.4)
65 to <85 years	16 (50.0)	15 (50.0)	31 (50.0)
≥85 years	1 (3.1)	0	1 (1.6)
Sex, n (%)			
Female	3 (9.4)	5 (16.7)	8 (12.9)
Male	29 (90.6)	25 (83.3)	54 (87.1)
Race, n (%)			
Asian	12 (37.5)	12 (40.0)	24 (38.7)
Caucasian	10 (31.3)	10 (33.3)	20 (32.3)
Unknown	10 (31.3)	8 (26.7)	18 (29.0)
ECOG PS, n (%)			
0	24 (75.0)	17 (56.7)	41 (66.1)
1	8 (25.0)	13 (43.3)	21 (33.9)
HCC aetiology, n (%)			
HBV	10 (31.2)	11 (36.7)	21 (33.9)
HBC	11 (34.4)	3 (10.0)	14 (22.6)
Non-viral	11 (34.4)	16 (53.3)	27 (43.5)
HBV status, n (%)			
Negative	22 (68.8)	19 (63.3)	41 (66.1)
Positive	10 (31.2)	11 (36.7)	21 (33.9)
HCV status, n (%)			
Negative	21 (65.6)	27 (90.0)	48 (77.4)
Positive	11 (34.4)	3 (10.0)	14 (22.6)
Portal vein invasion, n (%)			
No	22 (68.8)	20 (66.7)	42 (67.7)
Yes	8 (25.0)	8 (26.7)	16 (25.8)
Unknown	2 (6.3)	2 (6.7)	4 (6.5)
BCLC stage at study entry, n (%)			
B	7 (21.9)	4 (13.3)	11 (17.7)
C	25 (78.1)	26 (86.7)	51 (82.3)
Child–Pugh A total score at study entry, n (%)			
A5	28 (87.5)	18 (60.0)	46 (74.2)
A6	4 (12.5)	12 (40.0)	16 (25.8)
Creatinine, n (%)			
Normal	27 (84.4)	20 (66.7)	47 (75.8)
Low	3 (9.4)	8 (26.7)	11 (17.7)
High	2 (6.3)	2 (6.7)	4 (6.5)
Total bilirubin, n (%)			
Normal	22 (68.8)	26 (86.7)	48 (77.4)
Low	0	2 (6.7)	2 (3.2)
High	10 (31.3)	2 (6.7)	12 (19.4)
Most common metastatic sites[*,†], n, %			
Lung	9 (28.1)	10 (33.3)	19 (30.6)
Bone	4 (12.5)	9 (30.0)	13 (21.0)
Adrenal	6 (18.8)	2 (6.7)	8 (12.9)
Hepatic hilar lymph nodes	2 (6.3)	5 (16.7)	7 (11.3)
Peritoneum	4 (12.5)	3 (10.0)	7 (11.3)
Prior radiotherapy, n (%)	4 (12.5)	5 (16.7)	9 (14.5)
Prior surgery, n (%)	19 (59.4)	13 (43.3)	32 (51.6)

BCLC, Barcelona Clinic Liver Cancer; CRF, chronic renal failure; ECOG PS, Eastern Cooperative Oncology Group performance status; FAS, full analysis set; HBV, hepatitis B virus; HCV, hepatitis C virus; RP2D; recommended phase II dose.

[*] Metastatic sites with four or more patients in either of the two treatment arms, have been included in the table. Metastatic sites and number of organs involved are derived from CRF page of diagnosis and extent of cancer if available. Otherwise, they were derived from tumour assessment pages.

[†] Nine patients in the combination arm and five in the spartalizumab-alone arm were reported with 'no metastatic site'. Metastatic sites were classified as 'other' in nine and six patients from the combination and monotherapy arms, respectively.

Safety

The median duration of exposure to study treatment was 20.9 weeks (range: 3–97 weeks) in the combination arm and 15.9 weeks (range: 3–114 weeks) in the spartalizumab-alone arm. The cumulative dose, average dose, and relative dose intensity of capmatinib and spartalizumab treatments are summarised in Tables S3 and S4.

The overall safety data are summarised in Table S5. The most frequently reported AEs (>30%, any grade, regardless of relationship to study treatment) were peripheral oedema, decreased appetite, and nausea (46.9% each), asthenia and pyrexia (43.8% each), and diarrhoea (31.3%); grade ≥3 AEs (in >10% of patients, regardless of relationship to study treatment) were asthenia and ascites (18.8%, each), and increased lipase (15.6%) in the

Table 3. Investigator-assessed BOR, PFS, and OS per RECIST v1.1 in combination and monotherapy arms–Phase II (FAS).

Efficacy parameter	Capmatinib (RP2D) + spartalizumab n = 32	Spartalizumab n = 30
BOR, n (%)		
CR	0	0
PR	3 (9.4)	3 (10.0)
SD	12 (37.5)	9 (30.0)
PD	13 (40.6)	15 (50.0)
Unknown	4 (12.5)	3 (10.0)
ORR (CR + PR), n (%) [95% CI]	3 (9.4) [2.0–25.0]	3 (10.0) [2.1–26.5]
DCR (CR + PR + SD), n (%) [95% CI]	15 (46.9) [29.1–65.3]	12 (40.0) [22.7–59.4]
PFS		
Events, n (%)	30 (93.8)	26 (86.7)
Median (95% CI), months	2.79 (2.60–3.88)	2.79 (1.45–4.07)
OS		
Events, n (%)	23 (71.9)	22 (73.3)
Median (95% CI), months	14.88 (9.00–19.48)	9.79 (3.65–22.31)

BOR, best overall response; CI, confidence interval; CR, complete response; DCR, disease control rate; FAS, full analysis set; NA, not achieved; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours; RP2D; recommended phase II dose; PD, progressive disease; PR, partial response; SD, stable disease.

combination arm. In the spartalizumab-alone arm, increased AST (33.3%) was the most frequently reported AE (>30%, any grade, regardless of relationship to study treatment). The most common grade ≥3 AE (in >10% of patients, regardless of relationship to study treatment) was increased AST (13.3%, Table S6).

Overall, 93.8% TRAEs were reported in the combination arm *vs.* 60% in the spartalizumab-alone arm (Table S5). The TRAEs (≥20%, any grade) were nausea (37.5%), asthenia and vomiting (28.1% each), and diarrhoea, pyrexia, and decreased appetite (25.0% each) in the combination arm. The most frequent TRAEs (≥10%, any grade) in the spartalizumab-alone arm were pruritus (23.3%) and rash (10.0%) (Table 4).

Fourteen patients (43.8%) in the combination arm and 10 patients (33.3%) in the spartalizumab-alone arm reported at least one SAE regardless of relationship to study treatment. The most frequently reported SAEs (>5%, any grade) in the combination arm were ascites (15.6%) and pyrexia (9.4%); and in the spartalizumab-alone arm, pyrexia (6.7%) and blood bilirubin increased (6.7%). Treatment-related SAEs were reported in seven patients (21.9%) in the combination arm and one patient (3.3%) in the spartalizumab-alone arm.

The AEs leading to discontinuation reported in ≥5% of patients (any grade) in the combination arm included pyrexia (9.4%) and vomiting (6.3%). In the spartalizumab-alone arm, one patient (3.3%) reported abnormal liver function tests, which led to study treatment discontinuation; the event was not suspected to be related to study treatment. The most frequently reported AEs (any grade, ≥10%) leading to dose adjustment/interruption were asthenia (15.6%), diarrhoea, vomiting, and increased lipase (12.5% each) in the combination arm, and increased blood bilirubin (10.0%) in the spartalizumab-alone arm.

There were four on-treatment deaths (12.5%) in the combination arm, and all were attributed to the study indication. No on-treatment deaths were reported in the spartalizumab-alone arm.

PK analysis (phases Ib and II)

In phase Ib, capmatinib exposure in combination with spartalizumab (300 mg q3w) increased on increasing the capmatinib dose from 200 to 400 mg bid. The primary PK parameters of capmatinib on cycle 2 day 1 are summarised in detail in the Supplementary Results and Table S7.

In phase II, pre-dose capmatinib exposures were comparable from cycle 2 day 1 onward. Similarly, predose spartalizumab exposures were comparable from cycle 2 onward. The PK parameters of capmatinib in phase II are not summarised because of sparse sampling. The PK parameters of spartalizumab following the administration of spartalizumab 300 mg q3w in cycles 1 and 3 are summarised in Table S8. Overall, the spartalizumab exposure between the single agent and capmatinib combination arms was considered comparable, given the variability and limited sample size.

PD and biomarker analyses (for both phases)

The median CD8 and PD-L1 expression levels measured by immunohistochemistry (IHC) did not change significantly following treatment in both phase Ib and phase II. No clear trend in CD8 and PD-L1 expression was established. In addition, the number of patients analysed post-baseline was low. The results (CD8 and PD-L1 expression) of phase Ib and phase II are described in the Supplementary Results.

Whole transcriptome profiling by RNAseq was performed to search for a potential correlation with tumour response. A non-significant increase in interferon-γ (IFNg) and T-cell gene expression signatures was observed in on-treatment samples relative to baseline (data not shown).

Discussion

This is the first study to evaluate the combination of METi and PD-1 for the treatment of advanced HCC. In the phase Ib study, the RP2D for capmatinib in combination with spartalizumab 300 mg q3w was established at 400 mg bid. One DLT (grade 3 diarrhoea) was reported at the RP2D dose level and was adequately managed with supportive therapy. In this study, the TRAEs observed with the combination of capmatinib and spartalizumab were manageable and did not show significant safety concerns; however, a different study of this combination in advanced non-small cell lung cancer (aNSCLC) harbouring *MET* exon 14 skipping mutation observed high rates of TRAEs leading to study treatment dose reduction and/or interruption and TRAEs leading to treatment discontinuation, which ultimately led to the sponsor's decision to prematurely halt the study recruitment.[28] Another study evaluating capmatinib in

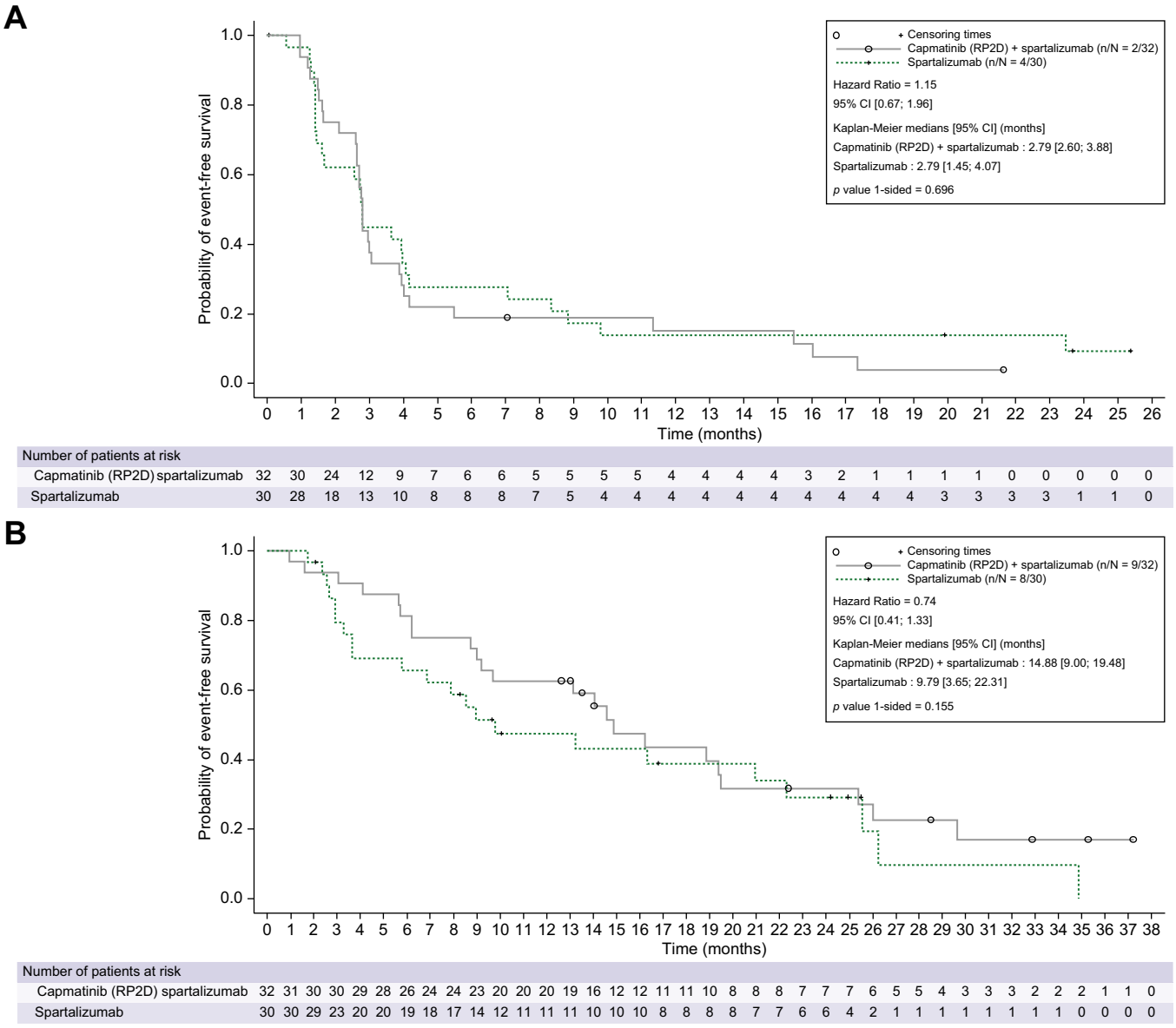

Fig. 3. Kaplan–Meier plots. (A) PFS per RECIST v1.1 and (B) OS –Phase II (FAS) Kaplan-Meier analysis was used to estimate the median and provide the Brookmeyer-Crowley 95% CI; estimated probabilities with corresponding 95% CI were calculated using Greenwood's formula. CI, confidence interval; FAS, full analysis set; OS, overall survival; PDR, plasma disappearance rate; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours; RP2D, recommended phase II dose.

combination with the PD-1 inhibitor pembrolizumab in high PD-1-expressing advanced NSCLC reported similar tolerability issues with high numbers of TRAEs, resulting in early termination of the trial.[29]

Preliminary clinical activity was observed during the phase Ib study (ORR at 14.8% and DCR at 51.9%) and these results were generally in line with the expected clinical activity seen in the second-line (2L) advanced HCC population.[22,23,30] However, the study's primary efficacy endpoint was not met in the phase II study. The observed ORR for the capmatinib + spartalizumab combination was 9.4%, and the observed ORR for spartalizumab alone was 10.0%; the combination treatment did not demonstrate superior antitumor effect compared with the spartalizumab single-agent treatment.

The PK profile of capmatinib in combination with spartalizumab was generally consistent with the known PK profiles of single-agent capmatinib and spartalizumab, respectively,[14,20] and did not suggest a PK drug-drug interaction. The cross-trial comparison with other 2L HCC studies involving PD-1 antibodies, KEYNOTE-224[31] and CheckMate 040,[23] showed that as single-agents, pembrolizumab and nivolumab had better median ORRs (17% and 14%, respectively) compared with the median ORRs in the capmatinib plus spartalizumab and spartalizumab-alone arms (9.4% and 10%, respectively) in our study. The median OS in the combination arm (14.88 months) and spartalizumab-alone arm (9.79 months) was consistent with that reported in KEYNOTE-224 (12.9 months)[31] and CheckMate 040 trials[23] (13.2 months). Baseline characteristics

Table 4. Treatment-related AEs (≥5%, any grade)–Phase II (safety set).

	Capmatinib (RP2D) + spartalizumab n = 32		Spartalizumab n = 30	
Preferred terms, n (%)	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Number of patients with at least one event	**30 (93.8)**	**18 (56.3)**	**18 (60.0)**	**3 (10.0)**
Nausea	12 (37.5)	0	1 (3.3)	0
Asthenia	9 (28.1)	6 (18.8)	2 (6.7)	1 (3.3)
Pruritus	3 (9.4)	0	7 (23.3)	0
Diarrhoea	8 (25.0)	1 (3.1)	1 (3.3)	0
Pyrexia	8 (25.0)	1 (3.1)	1 (3.3)	0
Vomiting	9 (28.1)	0	0	0
Decreased appetite	8 (25.0)	1 (3.1)	0	0
Chills	5 (15.6)	0	0	0
Increased lipase	4 (12.5)	4 (12.5)	0	0
Peripheral oedema	4 (12.5)	1 (3.1)	0	0
Fatigue	3 (9.4)	1 (3.1)	2 (6.7)	0
Rash	2 (6.3)	1 (3.1)	3 (10.0)	0
Abdominal distension	3 (9.4)	0	1 (3.3)	0
Myalgia	3 (9.4)	0	1 (3.3)	0
Dizziness	3 (9.4)	0	0	0
Headache	3 (9.4)	0	0	0
Rash maculo-papular	3 (9.4)	1 (3.1)	0	0
Dyspepsia	1 (3.1)	0	2 (6.7)	0
Upper abdominal pain	2 (6.3)	0	1 (3.3)	0
Increased amylase	2 (6.3)	1 (3.1)	1 (3.3)	0
Increased aspartate aminotransferase	2 (6.3)	1 (3.1)	2 (6.7)	1 (3.3)
Increased alanine aminotransferase	2 (6.3)	0	0	0
Increased blood bilirubin	2 (6.3)	0	0	0
Increased blood creatinine	2 (6.3)	0	0	0
Muscle spasms	2 (6.3)	0	0	0
Psoriasis	0	0	2 (6.7)	0
Stomatitis	2 (6.3)	0	0	0

A patient with multiple severity grades for an AE is only counted under the maximum grade. MedDRA version 24.0, CTCAE version 4.03. AE, adverse event; CTCAE, common terminology criteria for AEs; MedDRA, medical dictionary for regulatory activities; RP2D; recommended phase II dose.

were generally similar compared to the other clinical studies.[23,31–33] Unlike some trials,[5,34,35] the present study has included patients with main portal vein thrombosis. Patients with main portal vein thrombosis in HCC may show worse liver function, less treatment tolerance, and worse prognosis than those without.

Despite acknowledging the limitations of cross-trial comparison and the relatively short median follow-up for OS in this study, the outcomes of the present study compared fairly with the results of the other approved 2L targeted therapies. Pivotal trials evaluating the MKIs regorafenib[7] and cabozantinib[5] in patients treated with sorafenib demonstrated a median OS of 10.6 months and 10.2 months, and an ORR of 11% and 4%, respectively. Although sorafenib was the standard of care in patients with advanced HCC at the time of study design, the combination of atezolizumab and bevacizumab has since been approved as 1L therapy for patients with advanced HCC,[8] making 2L PD-1 monotherapy less relevant.

To date, no selective single targeted agents have shown promising efficacy outcomes in pivotal HCC trials. Tivantinib, a putative MET inhibitor, failed to improve OS compared with placebo in patients with MET-high with advanced HCC previously treated with sorafenib in a pivotal trial.[36] The preliminary efficacy findings from a phase Ib/II trial showed only modest antitumor activity of capmatinib in patients with *MET*-dysregulated advanced HCC, as defined by a MET IHC intensity score of 3+ in ≥50% of tumour cells or 2+ in ≥50% of tumour cells plus MET gene copy number ≥5 by fluorescence in situ hybridisation (FISH).[17] Tepotinib demonstrated a favourable benefit-risk profile in sorafenib-pre-treated HCC patients with MET overexpression in a phase I/II trial. However, it was a non-randomised, single--arm study with a small sample size and, therefore, the findings need to be validated in a larger sample size.[22] The MKI cabozantinib was recently approved for patients with advanced HCC previously treated with sorafenib;[5] however, carbozantinib is not a specific METi.

The study did not confirm our hypothesis that capmatinib in combination with spartalizumab could enhance the antitumor activity in HCC patients compared with spartalizumab as a single agent. Moreover, spartalizumab as a single-agent was not found to be clinically effective in HCC, which was consistent with previous immunotherapy studies[33,37] that also failed to show statistically significant improvements in their primary outcome measures. This highlights that PD-1 inhibitors when used as monotherapy are less effective against HCC, as was initially conceptualised.

The present study was designed to evaluate the therapeutic benefit of METi capmatinib in advanced HCC, based on evidence implicating the role of HGF-induced autocrine/paracrine activation of the MET pathway in the tumorigenesis of HCC.[11,12] However, the clinical outcomes in this study have not substantiated the potential of targeting the activated MET pathway to inhibit tumour growth in HCC. Furthermore, MET expression and MET status were not evaluated at the enrolment stage, as specific criteria of high dysregulation status of MET were not considered in the study design. However, an exploratory analysis was conducted to retrospectively assess MET status and it was found that the general patient population in the study had low MET expression status as defined by IHC and FISH, which could explain the lack of a better response from capmatinib in the

combination arm. A low incidence of MET-high disease in previously untreated patients with HCC was also reported in an earlier capmatinib study,[17] with only 5.2% of patients having tumours classified as MET-high.

Studying immune cell alterations in the tumour microenvironment that are induced by treatment with spartalizumab alone or by the combination of capmatinib and spartalizumab is critical to determine how capmatinib contributes to antitumor immune responses. Based on the limited number of tumour samples collected in this study, the PD data (CD8 and PD-L1 protein expression) did not show a significant change from baseline after treatment with capmatinib and spartalizumab or treatment with spartalizumab as a single agent. The RNA expression analyses showed a non-significant increase in IFNg and T-cell expression signatures in both treatment arms (data not shown). The absence of significant differences in the expression of these gene signatures between the two treatment arms supports the finding that the addition of capmatinib did not improve the antitumor activity of spartalizumab. This finding also supports the hypothesis that capmatinib treatment in combination with spartalizumab may have been more effective in a population selected for tumours high MET expressing tumours.

The study had some limitations, including (1) its design as an open-label, phase I/II study in a relatively small patient population; (2) the study population was unselected for MET—the study design was based on the tested hypothesis that blocking the MET pathway, regardless of MET pathway dysregulation status, would contribute to prevent HCC growth from the HGF-induced autocrine/paracrine activation; however, it appeared that autocrine/paracrine activation by HGF does not play a major role in driving HCC growth; and (3) there is a clear need to identify a reliable predictive marker of response in HCC and to identify the patient population that would benefit from the checkpoint inhibitor +/- targeted therapy combination for HCC. Despite these limitations, the choice to use a PD-1 inhibitor, a class of drugs with some clinical activity, as a comparator is worth noting, unlike other trials[7,21,30] where placebo/best supportive care was used for comparison.

In conclusion, the overall safety and tolerability results showed manageable toxicities and no new significant safety concerns were raised for the patients who participated in the study. Capmatinib at 400 mg bid in combination with spartalizumab 300 mg q3w was established as the RP2D, but the combination did not show superior clinical activity compared with spartalizumab single-agent treatment in patients with advanced HCC who had been previously treated with sorafenib. The modest clinical activity, along with the safety concerns and unfavourable benefit/risk profile reported in other NSCLC studies of capmatinib in combination with a PD-1 targeting agent, do not support the exploration of this combination, including as an indication for HCC.

Abbreviations

AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; bid, twice a day; BLRM, Bayesian logistic regression model; BOR, best overall response; CR, complete response; DCR, disease control rate; DLT, dose-limiting toxicity; EWOC, escalation with overdose control; FAS, full analysis set; HCC, hepatocellular carcinoma; irRC, immune-related response criteria; MedDRA, Medical Dictionary for Regulatory Activities; NA, not achieved; ORR, overall response rate; OS, overall survival; PD, pharmacodynamics; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PK, pharmacokinetics; PR, partial response; q3w, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumours; RP2D, recommended phase II dose; SD, stable disease; TTP, time to progression; TTR, time to response.

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Conflicts of interest

Please refer to the accompanying ICMJE disclosure forms for further details.

Author contributions

Conception and design: AS, AX, SLC. Data generation, collection, assembly, analysis and/or interpretation of data: AS, EA, TY, JD, MM, JK, SC, KL, GDC, CS, EL, AX, LF, FM, SLC. Writing, review, editing: AS, EA, TY, JD, MM, JK, SC, KL, GDC, CS, EL, AX, LF, FM, SLC. All authors contributed to the article and approved the submitted version.

Data availability statement

Novartis is committed to sharing with qualified external researchers, access to patient-level data, and supporting clinical documents from eligible studies. Requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided is anonymised 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 ClinicalStudyDataRequest.com.

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Supplementary data

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Author names in bold designate shared co-first authorship

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