Received: 25 September 2019 | Revised: 19 November 2019 | Accepted: 20 November 2019

DOI: 10.1111/cas.14254

ORIGINAL ARTICLE

Cancer Science WILEY

Phase 1 study of capmatinib in MET-positive solid tumor patients: Dose escalation and expansion of selected cohorts

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Abstract

Capmatinib is an oral, ATP-competitive, and highly potent, type 1b MET inhibitor. Herein, we report phase 1 dose-escalation results for capmatinib in advanced MET-positive solid tumor patients and dose expansion in advanced non-lung tumors. Capmatinib was well tolerated with a manageable safety profile across all explored doses. Dose-limiting toxicities (DLT) occurred at 200 mg twice daily (bid), 250 mg bid, and 450 mg bid capsules; however, no DLT were reported at 600 mg bid (capsules). Capmatinib tablets at 400 mg bid had comparable tolerability and exposure to that of 600 mg bid capsules. Maximum tolerated dose was not reached; recommended phase 2 dose was 400 mg bid tablets/600 mg bid capsules; at this dose, C_{trough} >EC_{90} (90% inhibition of c-MET phosphorylation in animal models) is expected to be achieved and maintained. Among the dose-expansion patients (N = 38), best overall response across all cohorts was stable disease (gastric cancer 22%, hepatocellular carcinoma 46%, other indications 28%); two other indication patients with gene copy number (GCN) ≥6 achieved substantial tumor reduction. Near-complete immunohistochemically determined phospho-MET inhibition (H-score = 2) was shown following capmatinib 450 mg bid capsule in paired biopsies obtained from one advanced colorectal cancer patient. Incidence of high-level *MET* GCN (GCN ≥6) and MET-overexpressing (immunohistochemistry 3+) tumors in the expansion cohorts was 8% and 13%, respectively; no *MET* mutations were observed. Thus, the recommended phase 2 dose (RP2D) of capmatinib was 600 mg bid capsule/400 mg bid tablet. Capmatinib was well tolerated and showed antitumor activity and acceptable safety profile at the RP2D.

Abbreviations: AE, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC_{tau}, area under plasma-concentration time curve over dosing interval; BIRC, blinded independent review committee; BLRM, Bayesian Logistic Regression Model; CI, confidence interval; C_{max}, maximum plasma concentration; CNS, central nervous system; CT, computed tomography; CV, coefficient of variation; DCR, disease control rate; DLT, dose-limiting toxicities; EGFR, epidermal growth factor receptor; EGFRwt, epidermal growth factor receptor wild-type; EWOC, escalation with overdose control; GBM, glioblastoma multiforme; GCN, gene copy number; HCC, hepatocellular carcinoma; HGF, hepatocyte growth factor; IHC, immunohistochemistry; LC-MS/MS, liquid chromatography-tandem mass spectrometry; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD, pharmacodynamics; PFS, progression-free survival; PK, pharmacokinetics; p-MET, phospho-MET; pRCC, papillary renal cell carcinoma; RP2D, recommended phase 2 dose; TKI, tyrosine kinase inhibitor; T_{max}, time to peak plasma concentration.

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Funding information
Novartis Pharmaceuticals Corporation

(ClinicalTrials.gov Identifier: NCT01324479).

KEYWORDS
capmatinib, MET amplification, MET dysregulation, phase 1, solid tumors

1 | INTRODUCTION

Dysregulation of MET signaling leads to activation of downstream pathways that include the RAS/MAPK, PI3K/AKT, and Rac/Rho pathways, promoting cell proliferation, survival, and metastasis.[1] MET dysregulation, through gene amplification, mutation, and/or overexpression has been described in multiple tumor types, including lung, HCC, GBM, pRCC, breast, colon, and gastric cancers.[1]

High-level *MET* gene amplification was originally described in gastric cancer cell lines,[2] resulting in increased mRNA and protein overexpression.[3] In *EGFRwt*, NSCLC de novo *MET* amplification has been reported in 1% to 4% of newly diagnosed cases.[4-6] *MET* amplification is also implicated in the acquired resistance to EGFR TKI, reported in 5% to 26% of cases, regardless of the presence of the *T790M* mutation.[7-13]

In addition, *MET* mutations have been identified in primary tumors as well as in metastatic lesions of several cancers, including head and neck, pRCC, liver, ovarian, and NSCLC.[14,15] In NSCLC, splice site alterations at exon 14 that lead to reduced internalization and degradation and net overexpression occur in 2% to 3% of adenocarcinomas[16-19] and in up to 22% of sarcomatoid NSCLC.[20]

Elevated levels of the receptor ligand HGF and/or overexpression of MET is often associated with resistance to chemotherapy and radiotherapy.[21] Overall, MET dysregulation is recognized as a negative prognostic factor, especially in advanced NSCLC[22-24] and is also associated with poor clinical outcomes in patients with glioblastoma and squamous cell carcinoma of the head and neck.[25,26]

Several MET inhibitors, comprising small molecule TKI and mAb targeting MET or its ligand, HGF, have been developed.[27] TKI are mainly divided into three types (I, II, and III) depending on binding of ATP to the MET kinase domain.[28,29] The apo-MET kinase adopts a distinctive autoinhibitory conformation (activation loop locks into the ATP binding site through a salt bridge between D1228 and K1110). Type I MET inhibitors are ATP-competitive, and bind to MET unique autoinhibitory conformation (π-stacking with Y1230 in the MET activation loop). Type I inhibitors are further divided into type Ia and type Ib. Potency of type Ia inhibitors is due to interaction with Y1230, the hinge, and the solvent front glycine residue G1163 (analogous to the same position as ALK G1202 and ROS1 G2032), whereas type Ib MET inhibitors have stronger interactions with Y1230 and the hinge, but not with G1163. Thus, type Ib inhibitors are highly specific for MET with fewer off-target effects compared with type Ia inhibitors. Type II inhibitors are ATP-competitive, but bind to the ATP adenine binding site extending to the hydrophobic back pocket. They distort the apo-MET autoinhibitory conformation and bind to an induced conformation. They do not have interaction with G1163. Type III inhibitors bind to allosteric sites different from the ATP binding site.[28] Capmatinib (INC280) is an oral, ATP-competitive and highly potent type 1b MET inhibitor in biochemical (IC_{50} 0.13 nmol/L) and cellular (IC_{50} ~ 1 nmol/L) assays and has proven to be highly selective versus other kinases in large panels of biochemical and binding assays.[30,31] Capmatinib caused regression of MET-dependent tumors at tolerable doses in animal models across a range of tumor types, including NSCLC, HCC, and GBM.[30,31] MET dependency in such responsive tumor models was associated with MET gene amplification (NSCLC, HCC), MET exon 14 skipping mutation (NSCLC), marked MET overexpression without amplification (NSCLC), or coexpression of MET and its ligand HGF (GBM).

The present phase 1 dose-escalation study (NCT01324479) assessed the safety and tolerability of capmatinib in patients with advanced MET-positive solid tumors. We also report herein the safety and efficacy observed in expansion cohorts of patients with MET-dysregulated gastric cancer, HCC, and other tumors (including GBM and pRCC). Safety and efficacy results of the expansion cohort of patients with advanced NSCLC is reported separately (Schuler M et al; manuscript submitted).

2 | MATERIALS AND METHODS

2.1 | Study design and treatment

This was a phase 1, open-label, multicenter, nonrandomized, two-part study comprising dose-escalation and expansion parts including patients with gastric cancer, HCC, and other solid tumor indications. In the first part of the study, molecularly prescreened patients with MET-dysregulated advanced solid tumors were enrolled in the dose-escalation phase. In the expansion phase, patients with solid tumors, including NSCLC, were enrolled based on MET dysregulation. Later, an additional expansion group was implemented to enrol patients with EGFR*wt* NSCLC preselected centrally

based on a high MET expression (IHC score 3+); results for the original NSCLC expansion group and additional expansion group are reported separately (Schuler M et al; manuscript submitted).

The primary objective of the present study was to determine the MTD/RP2D of oral capmatinib based on the incidence, frequency, and category of DLT in cycle 1 and the AE. A two-parameter BLRM using the EWOC principle[32,33] was used to guide the dose escalation for determination of the MTD or RP2D. Dose escalation was based on the incidence of DLT during cycle 1, with additional analyses carried out if significant toxicities were observed during later cycles (criteria for DLT provided in Table S1). After completion of a given cohort, the decision to dose escalate and the actual dose chosen depended on risk assessment calculations using the BLRM and medical review of available clinical and laboratory data, and the BLRM estimated the MTD by updating estimates of the probability of observing a DLT in the first cycle. For a given schedule, the MTD was defined as the highest drug dosage not expected to lead to DLT in >33% of patients in the first 28 days.

The key secondary endpoint was ORR by investigator assessment, defined as the proportion of subjects with measurable disease whose best overall response is either complete response or partial response according to the RECIST v1.1 or MacDonald criteria (only for GBM). Other secondary objectives were to further characterize antitumor activity, safety and tolerability, PK and PD (paired biopsies; IHC of p-MET, phospho-ERK, phospho-AKT, and phospho-S6, PK parameters), and DCR (proportion of patients whose best overall response is either complete response or partial response or stable disease).

In the dose-escalation part, separate cohorts of patients received treatment with increasing doses of capmatinib, starting at 100 mg bid in capsule formulation. PK and safety data from a tablet safety cohort were also used to guide the calculation of a tablet dose that would achieve comparable exposure to that of the RP2D of capmatinib capsules and meet the EWOC criteria in the BLRM for tablet. In the dose-expansion cohorts, patients were treated at a capmatinib dose of 600 mg bid, which is the RP2D of capmatinib capsules as determined in the safety cohort. Patients were permitted to switch to the 400 mg bid tablet dose. Patients were treated in 28-day cycles provided there was no evidence of disease progression or excessive toxicity and were continually reassessed for evidence of acute and cumulative toxicity.

2.2 | Patients

Adult patients (aged ≥18 years) with advanced solid tumors that are refractory to currently available therapies or for whom no effective treatment is available were eligible. Patients were required to have an ECOG Performance Status ≤2 and locally or centrally confirmed MET dysregulation as follows: for NSCLC, nasopharyngeal cancer, triple-negative breast cancer, pRCC, gastric cancer, and any other type of solid tumor, a MET H-score ≥150 or a ratio of MET/centromere ≥2.0 or MET GCN ≥5, or ≥50% of tumor cells with IHC score 2+ or score 3+; for HCC and GBM, a MET H-score ≥50 or a ratio of MET/centromere ≥2.0 or MET GCN ≥5. Patients with pRCC and germline MET mutation (in local report) were eligible. Key exclusion criteria were symptomatic CNS metastases that are neurologically unstable or requiring increasing doses of steroids to control; prior therapy with MET inhibitors or HGF-targeted therapy; or any CNS deficits (for GBM, CNS symptoms grade 2 or greater).

2.3 | Clinical assessments

Tumor lesions were assessed according to the RECIST v1.0 (investigator confirmed) or MacDonald criteria for patients with GBM. CT-based tumor assessments were carried out unless contraindicated or for GBM, in which case MRI with contrast was carried out. Assessments were carried out at screening, every 8 weeks beginning at the start of cycle 3 and as required to confirm response, and at the end of treatment (if no scan within 30 days prior to end of treatment). Safety assessments were carried out based on all AE, clinical laboratory data, and physical examinations.

2.4 | Pharmacokinetics analysis

During the phase 1 dose-escalation part of the study, pre-dose and 0.5, 1, 2, 4, 6, and 8 h post-dose PK samples were collected on cycle 1 day 1 and on cycle 1 day 15; pre-dose PK samples were collected on cycle 1 day 2, cycle 1 day 16, cycle 2 day 1, and cycle 3 day 1. During the phase 1 dose-expansion part of the study, pre-dose and 0.5, 1, 2, 4, 6, and 8 h post-dose PK samples were collected on cycle 1 day 15 in non-NSCLC patients; pre-dose PK samples were collected on cycle 1 day 16 and cycle 2 day 1. Capmatinib concentrations in plasma were measured using a validated LC-MS/MS method with a lower limit of quantification of 1 ng/mL. Noncompartmental PK analysis was done to generate PK parameters of capmatinib, and dose proportionality of capmatinib was assessed.

2.5 | Statistical analysis

Data cutoff date for this report was July 17, 2017 when all patients had discontinued. No formal statistical power calculations to determine sample size were carried out for this study. It was estimated that a minimum of 15 subjects would be enrolled in the dose-escalation phase, including at least six subjects treated at the MTD/RP2D level. During the expansion phase, subjects with HCC, NSCLC, or gastric cancer were enrolled into separate groups of 10 subjects each. Each of these three groups could be expanded by 15 additional subjects for a maximum of 25 subjects per group if additional insight into the safety and/or efficacy was desired. Decision for such expansion of a group was to be made no later than 16 weeks from initial treatment of the last subject for that group and by the Novartis Clinical Trial Team in consultation with the study investigators after reviewing all available clinical data. A fourth group was expected to enrol up to 15 subjects with other solid tumors (pRCC, GBM, and others).

TABLE 1 Patient demographics and disease characteristics in the dose-escalation and selected dose-expansion cohorts

		Expansion (RP2D)			
	Dose escalation (N = 38)	Gastric cancer n = 9	HCC n = 11	Other indications n = 18	All expansion (N = 38)
Age (median, y)	56.0	55.0	54.0	57.0	55.3
Age category (years), n (%)					
<65	32 (84)	9 (100)	8 (73)	13 (72)	30 (79)
≥65	6 (16)	0	3 (27)	5 (28)	8 (21)
Gender (male, n [%])	27 (71)	7 (78)	9 (82)	15 (83)	31 (82)
Race					
Caucasian	6 (16)	9 (100)	6 (55)	13 (72)	28 (74)
Asian	31 (82)	0	4 (36)	1 (6)	5 (13)
Other	1 (3)	0	1 (9)	4 (22)	5 (13)
ECOG PS, n (%)					
0	21 (55)	3 (33)	7 (64)	10 (56)	20 (53)
1	16 (42)	6 (67)	4 (36)	6 (33)	16 (42)
2	1 (3)	0	0	1 (6)	1 (3)
Missing	0	0	0	1 (6)	1 (3)
Primary site of cancer					
Liver	15 (39)	0	11 (100)	0	11 (29)
Colon	8 (21)	0	0	0	0
Stomach	2 (5)	9 (100)	0	0	9 (24)
Lung	1 (3)	0	0	0	0
Other	12 (32)	0	0	18 (100)	18 (47)
No. of prior lines of therapy, n (%)					
Missing	0	0	0	2 (11)	2 (5)
1	6 (16)	2 (22)	6 (55)	4 (22)	12 (32)
2	7 (18)	1 (11)	2 (18)	2 (11)	5 (13)
≥3	25 (66)	6 (67)	3 (27)	10 (56)	19 (50)

Abbreviations: bid, twice daily; ECOG PS, ECOG performance status; HCC, hepatocellular carcinoma; RP2D, recommended phase 2 dose.

The ORR was presented by treatment group with an exact 95% CI if response rate of 10% or higher was observed. Kaplan-Meier estimate of median PFS and rate at 3, 6, and 12 months, along with 95% CI, were summarized by treatment group according to the investigator and BIRC. A waterfall plot of best percentage change from baseline in sum of longest diameters according to the investigator was presented for each treatment group. AE were graded according to the Common Terminology Criteria for Adverse Events, version 4.0.

For dose-escalation, a BLRM (with two parameters) guided by the EWOC principle was used to make dose recommendations and to estimate the MTD. When the change from capsule to tablet formulation was implemented, a BLRM for the tablet formulation was set up and used to monitor subject safety. Prior distributions for this model incorporated the existing dose toxicity data for capmatinib as single agent in both capsule and tablet formulations. The posterior distributions for the risk of DLT were summarized to provide the posterior probability that the risk of DLT lies within the following intervals: [0, 0.16) underdosing, [0.16, 0.33) targeted toxicity, and [0.33, 1.00] excessive toxicity.

For secondary efficacy and safety endpoints, patients treated at the RP2D for capmatinib during the escalation phase were pooled with those receiving the same dosing regimen and with same disease during the expansion phase. Safety data are summarized for all the patients who received at least one dose of capmatinib and had at least one valid postbaseline safety assessment. The dose determining set consisted of all subjects from the safety set who either met the minimum exposure criterion (capmatinib had been given at the full planned daily dose for ≥21 days out of 28 days [75%] and the subject had sufficient safety evaluations, or had experienced a DLT during the first cycle). Efficacy data are summarized for all the patients with NSCLC who received at least one dose of capmatinib. PK analyses were based on data from patients in the dose-escalation phase and expansion phase, with at least one evaluable capmatinib PK profile.

TABLE 2 Assessment of MET overexpression by IHC and GCN by FISH for patients in the dose-escalation and selected dose-expansion cohorts

	Dose escalation, mg bid					Dose expansion			
	100-350 n = 16	450 n = 9	600 n = 8	400 (tablet) n = 5	All escalations N = 38	Gastric cancer n = 9	HCC n = 11	Other indications n = 18	All expansions N = 38
IHC score, n (%)*	N = 15	N = 9	N = 8	N = 4	N = 36	N = 9	N = 8	N = 11	N = 28
0	2	1	1	1	5 (13.9)	2	2	1	5 (17.9)
1+	7	3	2	2	14 (38.9)	2	3	4	9 (32)
2+	2	3	5	1	11 (30.6)	2	2	5	9 (32)
3+	4	2	0	0	6 (16.7)	3	1	1	5 (17.9)
MET GCN n (%)*	N = 6	N = 6	N = 8	N = 3	N = 23	N = 7	N = 6	N = 17	N = 31
<4	3	4	4	3	14 (60.9)	5	5	12	22 (71.0)
≥4-<6	1	2	3	0	6 (26.1)	2	1	2	6 (19.4)
≥6	2	0	1	0	3 (13.0)	0	0	3	3 (9.7)

Abbreviations: bid, twice daily; FISH, fluorescence in situ hybridization; GCN, gene copy number, HCC, hepatocellular carcinoma; IHC, immunohistochemistry.

*Denominator for calculating percentages equals number of known results.

2.6 | Study oversight

This study was carried out in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. The protocol was approved by an Institutional Review Board at each hospital or site, and all patients provided written informed consent before any study procedures. The study was designed by the sponsor (Novartis Pharma AG). Data were collected and analyzed by the sponsor in conjunction with the authors.

3 | RESULTS

A total of 38 patients (with HCC [n = 15], colon [n = 8], gastric [n = 2], lung [n = 1], and other advanced solid tumor types [n = 12]) were enrolled into the dose-escalation part of this phase 1 study and 38 patients (with HCC [n = 11], gastric [n = 9], and other advanced solid tumor types [non-NSCLC; n = 18]) were enrolled into the expansion cohorts (Table 1). Fifty-five patients with NSCLC were also enrolled into an additional expansion cohort; results of these patients are reported separately (Schuler M et al; manuscript submitted).

In the dose-escalation cohort, 19 of 38 (50%) patients received ≥3 prior lines of therapy. Of the 23 evaluable patients, 26.1% had tumors presenting with a high level of *MET* gene copy gain (GCN ≥6) and 16.7% of the 36 evaluable patients had *MET*-overexpressing tumors (IHC score 3+).

In the dose-expansion part, the majority of patients were heavily pretreated, with 25 of 38 (66%) patients having received ≥3 prior lines of therapy. Of the patients enrolled in the selected expansion cohorts, where results were available (n = 31), 9.7% of patients had tumors presenting with high-level *MET* GCN and 13% of the 38 evaluable patients had *MET*-overexpressing tumors (Table 2). None of the patients had tumors harboring *MET* exon 14 skipping mutations or other *MET* mutations known to confer sensitivity to MET inhibitors.

In the escalation part, capmatinib capsules were evaluated at the following twice-daily (bid) doses: 100 mg (n = 4), 200 mg (n = 5), 250 mg (n = 4), 350 mg (n = 3), 450 mg (n = 9), and 600 mg (n = 8). In order to improve patient compliance in reducing pill burden, a tablet formulation was then introduced. Capmatinib in tablet formulation was evaluated at the RP2D 400 mg bid (n = 5). In the dose-expansion part, patients were enrolled at the RP2D of capmatinib, 600 mg bid, in capsule formulation. Seven patients treated with capmatinib in capsule formulation switched to the tablet formulation once it became available.

As of July 17, 2017, all patients in the dose-escalation and selected cohorts of the dose-expansion part of the study had discontinued treatment. Primary reason for end of treatment was disease progression (37 of 38 patients [97%] in the dose-escalation part and 29 of 38 patients [76%] in the dose-expansion part). One patient discontinued as a result of AE (AST increase) in the dose-escalation part and six of 38 patients (16%) in the dose-expansion part (as a result of thrombocytopenia [n = 1], nausea [n =

1], nausea/vomiting [n = 1], nausea/dizziness [n = 1], pneumonia [n = 1], and peripheral edema [n = 1]). Reasons for discontinuation for the remaining patients in the selected cohorts of the dose-expansion part were consent withdrawal (2 patients) and protocol deviation (1 patient). No patients discontinued as a result of death in either part of the study.

3.1 | Dose determination

Starting dose for dose escalation of this study was 100 mg bid as capsules. The bid regimen was selected based on the half-life of capmatinib (3.5-6.3 h) and in order to maintain capmatinib concentrations above the EC_{90} (90% inhibition of c-MET phosphorylation in animal models) for p-MET inhibition in c-MET-dependent mouse tumor models (EC_{90} ~71 nmol/L, total concentration).[30] Across the six bid dose levels explored in the capsule formulation, DLT occurred at 200 mg bid (grade 3 fatigue in 1 patient), 250 mg bid (grade 3 bilirubin increased in 1 patient), and 450 mg bid (grade 3 fatigue in 1 patient). No DLT were observed at the 600-mg bid capsule dose level. Based on the BLRM used to guide dose escalation, posterior probability of excessive toxicity was 20.1% for the 600 mg bid dose level in the dose-escalation phase (ie, <25% chance that the true DLT rate was ≥33%). No DLT was observed among patients treated with the tablet at the 400 mg bid dose. MTD was not reached. Capmatinib tablets at 400 mg bid had comparable tolerability and exposure to that of 600 mg bid capsules. Capmatinib 400 mg bid tablets or 600 mg bid capsules were selected as the RP2D, a dose at which C_{trough} >EC_{90} (90% inhibition of c-MET phosphorylation in animal models) is expected to be achieved and maintained.

3.2 | Safety

The most frequent AE (all grades, >30%) in the dose-escalation part regardless of causality were decreased appetite (42%), peripheral edema (40%), vomiting (40%), and nausea (37%) (Table S2). The most frequent grade 3 or 4 AE (>5%) regardless of causality were increase in levels of blood bilirubin (11%), fatigue (8%), and AST increase (8%). The most common AE (all grades, >20%) suspected to be study drug-related were nausea (32%), decreased appetite (29%), vomiting (29%), fatigue (26%), and peripheral edema (21%) (Table 3). Study drug-related grade 3 or 4 AE were rare. The most commonly reported AE were fatigue (8%), ALT increase, and hypophagia (both 5%).

In the selected cohorts of the dose-expansion part of the study, the most frequent AE (all grades, >30%) regardless of causality were nausea (42%), peripheral edema (39%), and fatigue (34%) (Table S2). The most frequent grade 3 or 4 AE regardless of causality were fatigue (8%), nausea, AST increase, anemia, ascites, bilirubin increase, constipation, and ALT increase (all 5%).

Nausea (29%), peripheral edema (26%), and fatigue (24%) were the most common AE suspected to be study drug-related (Table 3). ALT and lipase increases were the most commonly reported grade 3 or 4 AE suspected to be study drug-related (both 5%).

3.3 | Efficacy

Efficacy was reported according to the investigator's assessment. In the dose-escalation part of the study, at the data cutoff date of July 17, 2017, stable disease was reported in 10 of 38 (26%) patients (Table 4). In the dose-escalation part, tumor shrinkage was observed in two patients (colon cancer and HCC) treated at 450 mg bid (capsule) dose level.

Efficacy results in the expansion cohorts of patients with gastric cancer, HCC, and other solid tumors (non-NSCLC including GBM and pRCC) are presented in Table 4. In these cohorts, stable disease was reported in two of nine (22%) patients with gastric cancer, five of 11 (46%) patients with HCC, and five of 18 (28%) patients with other advanced solid tumor types. Tumor reduction was reported in a number of patients; of note, two other solid tumor patients with GCN ≥6 achieved substantial tumor reduction (Figure 1). Duration of response for evaluable patients by disease cohorts is shown in Figure S1.

3.4 | Pharmacokinetics analysis

Capmatinib was rapidly absorbed after oral dose, with median time to peak plasma concentration (T_{max}) ranging from 1 to 4 h for capsules and approximately 2 h for tablets following single and multiple doses (Table 5).

Steady-state AUC_{tau} and C_{max} of capmatinib were generally dose proportional across the dose range from 100 to 600 mg bid for the capsules (Table 5). The drug accumulation ratio following multiple doses generally ranged from one- to twofold for the capsules, with more accumulation observed at 450 and 600 mg bid (ca. twofold). Limited drug accumulation was observed with 400 mg bid tablets (Table 6).

Tablet formulation at 400 mg bid provided comparable mean exposures to the capsules at 600 mg bid (Table 5). Mean (mean CV%) steady-state exposure of capmatinib at the RP2D (tablet 400 mg bid) was 22 000 (35.5%) h*ng/mL for $AUC_{0-12\ h,ss}$ and 4910 (51.0%) ng/mL for $C_{max,ss}$ (n = 8).

3.5 | Pharmacodynamic data

Capmatinib PD activity in inhibiting the MET pathway was shown in paired biopsies collected from a patient with advanced CRC. Near-complete p-MET inhibition (as determined by IHC; H-score = 2) was shown following capmatinib at 450 mg bid in capsule formulation at cycle 1 day 15 (Figure S2).

4 | DISCUSSION

Capmatinib was well tolerated with a manageable safety profile across all explored doses. Only three DLT were reported, one each

TABLE 3 Adverse events, suspected to be study drug related (any grade occurring in ≥5% of patients in either the dose-escalation or selected dose-expansion cohorts and grade 3 or 4)

	Dose escalation, mg bid										Dose expansion (RP2D)							
	100-350 n = 16		450 n = 9		600 n = 8		400 (tablet) n = 5		All N = 38		Gastric cancer n = 9		HCC n = 11		Other n = 18		All expansions N = 38	
Preferred Term	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Nausea	3 (19)	0	4 (44)	0	3 (38)	0	2 (40)	0	12 (32)	0	0	0	5 (46)	1 (9)	6 (33)	0	11 (29)	1 (3)
Decreased appetite	5 (31)	1 (6)	3 (33)	0	3 (38)	0	0	0	11 (29)	1 (2)	0	0	2 (18)	0	2 (11)	0	4 (11)	0
Vomiting	4 (25)	0	3 (33)	0	3 (38)	0	1 (20)	0	11 (29)	0	0	0	3 (27)	1 (9)	4 (22)	0	7 (18)	1 (3)
Fatigue	3 (19)	2 (13)	3 (33)	1 (11)	3 (38)	0	1 (20)	0	10 (26)	3 (8)	3 (33)	1 (11)	3 (27)	0	3 (17)	0	9 (24)	1 (3)
Peripheral edema	3 (19)	1 (6)	2 (22)	0	1 (13)	0	2 (40)	0	8 (21)	1 (3)	3 (33)	0	3 (27)	0	4 (22)	0	10 (26)	0
Asthenia	4 (25)	0	1 (11)	0	0	0	1 (20)	0	6 (16)	0	0	0	1 (9)	0	1 (6)	0	2 (5)	0
Hypoalbuminemia	3 (19)	1 (6)	0	0	1 (13)	0	2 (40)	0	6 (16)	1 (3)	0	0	0	0	1 (6)	0	1 (3)	0
AST increased	1 (6)	0	1 (11)	1 (11)	2 (25)	0	1 (20)	0	5 (13)	1 (3)	1 (11)	0	1 (9)	1 (9)	2 (11)	0	4 (11)	0
Diarrhea	2 (13)	0	0	0	2 (25)	0	1 (20)	0	5 (13)	0	0	0	4 (36)	0	3 (17)	0	7 (18)	0
Blood bilirubin increased	3 (19)	1 (6)	0	0	1 (13)	0	0	0	4 (11)	1 (3)	0	0	0	0	0	0	0	0
ALT increased	0	0	1 (11)	1 (11)	1 (13)	1 (13)	1 (20)	0	3 (8)	2 (5)	1 (11)	1 (11)	0	0	1 (6)	1 (6)	2 (5)	2 (5)
Constipation	2 (13)	0	0	0	0	0	1 (20)	0	3 (8)	0	0	0	0	0	1 (6)	0	1 (3)	0
Upper abdominal pain	1 (6)	0	0	0	0	0	1 (20)	0	2 (5)	0	0	0	0	0	0	0	0	0
Amylase increased	2 (13)	1 (6)	0	0	0	0	0	0	2 (5)	1 (3)	0	0	0	0	0	0	0	0
Blood creatinine increased	2 (13)	0	0	0	0	0	0	0	2 (5)	0	0	0	1 (9)	1 (9)	1 (6)	0	2 (5)	1 (3)
Headache	1 (6)	0	1 (11)	0	0	0	0	0	2 (5)	0	1 (11)	0	0	0	0	0	1 (3)	0
Hypophagia	2 (13)	2 (13)	0	0	0	0	0	0	2 (5)	2 (5)								
Myalgia	2 (13)	0	0	0	0	0	0	0	2 (5)	0	0	0	0	0	2 (11)	0	2 (5)	0
Odynophagia	1 (6)	0	0	0	0	0	1 (20)	0	2 (5)	0	0	0	0	0	0	0	0	0
Total protein decreased	1 (6)	0	0	0	1 (13)	0	0	0	2 (5)	0	0	0	0	0	0	0	0	0
Pyrexia	1 (6)	0	1 (11)	0	0	0	0	0	2 (5)	0	0	0	0	0	0	0	0	0
Stomatitis	0	0	0	0	1 (13)	0	1 (20)	0	2 (5)	0	0	0	0	0	1 (6)	0	1 (3)	0
Lipase increased	1 (6)	1 (6)	0	0	0	0	0	0	1 (3)	1 (3)	0	0	2 (18)	2 (18)	1 (6)	0	3 (8)	2 (5)
Dyspepsia	0	0	0	0	1 (13)	0	0	0	1 (3)	0	0	0	0	0	2 (11)	0	2 (5)	0
Thrombocytopenia	1 (6)	0	0	0	0	0	0	0	1 (3)	0	1 (11)	1 (11)	1 (9)	0	0	0	2 (5)	1 (3)
Dizziness	0	0	0	0	0	0	1 (20)	0	1 (3)	0	0	0	1 (9)	0	1 (6)	0	2 (5)	0
Maculo-papular rash	0	0	1 (11)	0	0	0	0	0	1 (3)	0	0	0	0	0	2 (11)	0	2 (5)	0
Localized edema											0	0	0	0	2 (11)	0	2 (5)	0

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; bid, twice daily; HCC, hepatocellular carcinoma; RP2D, recommended phase 2 dose.

TABLE 4 Best overall response by treatment group according to investigator in the dose-escalation and selected dose-expansion cohorts

	Dose escalation, mg bid							Dose expansion (RP2D)			
	100 n = 4	200 n = 5	250 n = 4	350 n = 3	450 n = 9	600 n = 8	400 (tablet) n = 5	All escalations N = 38	Gastric cancer n = 9	HCC n = 11	Other indications n = 18	All expansions N = 38
Best overall response, n (%)												
Complete response	0	0	0	0	0	0	0	0	0	0	0	0
Partial response	0	0	0	0	0	0	0	0	0	0	0	0
Stable disease	2 (50)	1 (20)	1 (25)	1 (33)	2 (22)	1 (13)	2 (40)	10 (26)	2 (22)	5 (46)	5 (28)	10 (26)
Progressive disease	2 (50)	4 (80)	2 50)	2 (67)	6 (67)	6 (75)	3 (60)	25 (66)	3 (33)	1 (9.1)	9 (50)	26 (68)
Unknown	0	0	1 (25)	0	1 (11)	1 (13)	0	3 (5)	4 (44)	5 (46)	4 (22)	2 (5)
Overall response rate, n (%) 95% CI	0 0.0-60.2	0 0.0-52.2	0 0.0-60.2	0 0.0-70.8	0 0.0-36.9	0 0.0-36.9	0 0.0-52.2	0 0.0-9.3	0 0.0-33.6	0 0.0-28.5	0 0.0-18.5	0 0.0-9.3
Disease control rate, n (%) 95% CI	2 (50) 6.8-93.2	1 (20) 0.5-71.6	1 (25) 0.6-80.6	1 (33) 0.8-90.6	2 (22) 2.8-60.0	1 (13) 0.3-52.7	2 (40) 5.3-85.3	10 (26) 13.4-43.1	2 (22.2) 2.8-60.0	5 (45.5) 16.7-76.6	5 (27.8) 9.7-53.5	10 (26) 13.4-43.1

Abbreviations: bid, twice daily; CI, confidence interval; HCC, hepatocellular carcinoma; RP2D, recommended phase 2 dose.

at 200 mg bid, 250 mg bid, and 450 mg bid doses. No DLT were observed at the 600-mg bid capsule dose level. Based on the BLRM used to guide dose escalation, the posterior probability of excessive toxicity was 20.1% for the 600-mg bid dose level in the dose-escalation phase. Capmatinib exposure was found to increase by dose up to 600 mg bid dose level.

In the dose-escalation part, tumor shrinkage was observed for two patients (colon cancer and HCC) treated with the 450-mg bid (capsule) dose level. Near-complete PD effect (defined as p-MET inhibition) was observed in this patient with colorectal cancer at 450-mg bid capsule dose level. MTD was not reached. Thus, based on considerations of the estimated MTD by the BLRM model along with overall assessment of safety, PK and PD results, and preliminary clinical efficacy data, the RP2D was determined initially to be 600 mg bid in capsule formulation.

In order to improve patient compliance reducing the pill burden, a tablet formulation was introduced, as 12 capsules had to be taken bid as the 600 mg bid dose regimen. Relative bioavailability of INC280 tablet with respect to capsule formulation was assessed in healthy subjects, and a tablet safety cohort at 400 mg bid was further evaluated in this study. The evaluated tablet formulation at a dose of 400 mg bid was well tolerated with no DLT reported, had a comparable favorable safety profile, and comparable mean exposure to the capsule formulation at a dose of 600 mg bid. Thus, the RP2D was determined to be 400 mg bid in tablet formulation. A number of the expansion-part patients were switched from the capsule formulation to the tablet as soon as it was available.

Overall, capmatinib was well tolerated at the RP2D (600 mg bid capsule and 400 mg bid tablet). The most common AE suspected to be related to the study drug were mostly grade 1 or 2.

Only a limited number of patients were determined to have tumors harboring high-level *MET* gene copy gain or high *MET* overexpression or *MET* mutations in both the escalation and selected expansion cohorts. Although the best overall response was limited with stable disease in 26% of escalation patients and in 32% of the expansion patients (22% of patients in the gastric cancer cohort, 46% of patients in the HCC cohort, and 28% of patients with other advanced solid tumor types), a number of these patients achieved substantial tumor reduction and durable stable disease; of note, two other solid tumor patients with GCN ≥6 achieved substantial tumor reduction (Figure 1). These results were similar to those observed with capmatinib with Japanese patients with advanced solid tumors, where the best overall response was stable disease (reported in 18.2% of patients).[34] BOI-9016M, a novel c-MET inhibitor, showed activity in Chinese patients with advanced solid tumors, with partial response in one (5%) of 20 patients and stable disease in 10 (50%) patients.[35] Results for other MET inhibitors have been reported in molecularly selected patients with NSCLC. Crizotinib, a multikinase (ALK/ROS1/MET) inhibitor, showed clinically meaningful antitumor activity in patients with *MET* exon 14-mutated NSCLC, with an ORR of 32% (21 of 65 patients; 95% CI: 21-45)[36] and in patients with high MET amplification (MET/CEP7 ≥4) status, with an ORR of 40% (eight of 20 patients; 95% CI: 19.1-63.9).[37] Tepotinib, a selective MET inhibitor, showed activity with an ORR of 57.5% (23 of 40 patients; 95% CI: 40.9-73.0) by the investigator in patients with advanced NSCLC harboring *MET exon 14 skipping* mutations.[38]

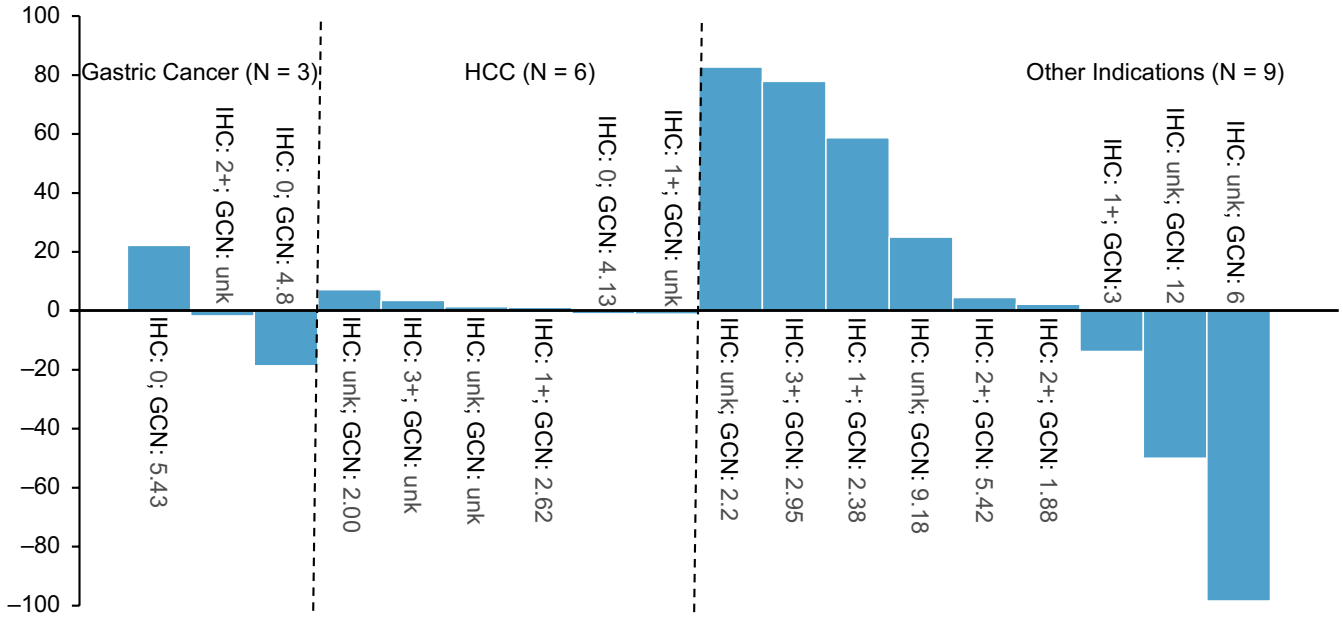

FIGURE 1 Best percentage change from baseline in sum of tumor diameters according to investigator assessment in dose-expansion cohorts (N = 18)*. *Patients with measurable baseline disease and at least one valid postbaseline (BIRC) assessment (best percentage change from baseline <0 [n = 7] and >0 [n = 11]).
BIRC, blinded independent review committee; GCN, gene copy number; HCC, hepatocellular carcinoma; IHC, immunohistochemistry; unk, unknown.

TABLE 5 Summary of steady-state PK parameters for capmatinib

	PK analysis set: dose group, mg bid						
PK parameter (Cycle 1, Day 15)	**100 n = 4**	**200 n = 5**	**250 n = 3**	**350 n = 3**	**450 n = 7**	**600 n = 45**	**400 (tablet) n = 8**
$AUC_{0-12\,h}$ (h*ng/mL)							
Mean (SD)	3820 (2420)	13 500 (6530)	7070 (3990)	19 400 (5360)	18 800 (6870)	25 600 (14 900)	22 000 (7790)
CV% mean	63.5	48.5	56.4	27.7	36.6	58.3	35.5
C_{max} (ng/mL)							
Mean (SD)	660 (550)	2500 (856)	1580 (1010)	4410 (3800)	3200 (1280)	4890 (3580)	4910 (2510)
CV% mean	83.3	34.2	63.8	86.3	39.8	73.2	51.0
T_{max} (h)							
Median	2.86	1.92	1.00	3.93	2.00	2.00	2.02
(Min; Max)	(1.88; 4.00)	(1.85; 8.00)	(0.45; 2.02)	(1.00; 4.02)	(1.83; 7.87)	(0.517; 8.42)	(0.50; 4.33)

Abbreviations: $AUC_{0-12\,h}$, area under concentration-time curve from time 0 to 12 h; bid, twice daily; C_{max}, maximum observed plasma concentration; CV%, percent coefficient of variation; T_{max}, median time to peak plasma concentration; PK, pharmacokinetics.

TABLE 6 Summary of accumulation ratio for capmatinib following repeated dosage

	PK analysis set: dose group, mg bid						
PK parameter (Cycle 1, Day 15)	**100 n = 3**	**200 n = 5**	**250 n = 3**	**350 n = 3**	**450 n = 5**	**600 n = 15**	**400 (tablet) n = 5**
Racc							
Mean (SD)	1.54 (0.786)	1.36 (0.869)	1.08 (0.443)	1.38 (0.614)	2.36 (1.75)	2.07 (0.848)	1.09 (0.408)
CV% mean	50.9	63.9	40.8	44.5	74.0	40.9	37.6

Abbreviations: bid, twice daily; CV%, percent coefficient of variation; PK, pharmacokinetics; Racc, mean accumulation ratio; ss, at steady state.

Overall, in the present study, suboptimal molecular selection for MET status might have contributed to the limited efficacy observed in both the escalation and the expansion cohorts of patients with gastric cancer, HCC, and other solid tumors.

Results of the expansion part of the study conducted with capmatinib at the RP2D in patients with advanced MET-dependent NSCLC, including a subset of patients enrolled with more stringently specified MET dysregulation biomarker criteria, are reported separately (Schuler M et al; manuscript submitted). Further, the predictive value of different mechanisms of MET dysregulation (including MET amplification and METΔex14 mutation) in advanced NSCLC is prospectively being explored in another ongoing phase 2 study of capmatinib (NCT02414139).

In summary, the RP2D of capmatinib was 600 mg bid capsule or 400 mg bid tablet. The tablet formulation is now used in all capmatinib studies. Capmatinib was well tolerated and showed antitumor activity and acceptable safety profile at the R2PD.

ACKNOWLEDGMENTS

We would like to take this opportunity to thank the participating patients, their families, all of the study co-investigators, and research contributors. Medical writing support was provided by Pushkar Narvilkar, Novartis Healthcare Pvt Ltd (Hyderabad, India) and Helen Garside (ex-Articulate Science employee). This study was funded by Novartis Pharmaceuticals Corporation.

CONFLICTS OF INTEREST

Annual value of remuneration received:

- Mikhail Akimov from Novartis (employment).
- Samson Ghebremariam from Novartis (employment).
- Monica Giovannini (self) from Novartis (employment).
- Monica Giovannini (family member) from Bluebirdbio (employment).

Annual profit from shares received:

- Mikhail Akimov has Novartis Stock.
- Samson Ghebremariam has Novartis Stock.
- Monica Giovannini (self) has Novartis Stock.
- Monica Giovannini (family member) has Bluebirdbio Stock.

Total annual value of daily allowances/honoraria received:

- David Hong from AbbVie (research grants), Adaptimmune (research grants, and consulting or advisory role), Amgen (research grants), AstraZeneca (research grants), Bayer (research grants, and consulting or advisory role), BMS (research grants), Daiichi Sankyo (research grants), Eisai (research grants), Fate Therapeutics (research grants), Genentech (research grants, consulting or advisory role), Genmab (research grants), Ignyta (research grants), Infinity (research grants), Kite (research grants), Kyowa (research grants), Lilly (research grants), LOXO (research grants), Merck (research grants), MedImmune (research grants), Mirati (research grants), MiRNA (research grants), Molecular Templates (research grants), Mologen (research grants), NCI-CTEP (research grants), Novartis (research grants), Pfizer (research grants, and consulting or advisory role), Seattle Genetics (research grants, and consulting or advisory role), Takeda (research grants, and consulting or advisory role), Alpha Insights (consulting or advisory role), Axiom (consulting or advisory role), Baxter (consulting or advisory role), GLG (consulting or advisory role), Group H (consulting or advisory role), Guidepoint Global (consulting or advisory role), Infinity (consulting or advisory role), Janssen (consulting or advisory role), Merrimack (consulting or advisory role), Medscape (consulting or advisory role), Numab (consulting or advisory role), and Trieza Therapeutics (consulting or advisory role).

Total annual value of manuscript fees received:

- Todd M. Bauer from Pfizer (paid to third part vendor for medical writing/editorial support).

Total annual value of research funds, endowments, endowed chairs, and researcher-employment costs received:

- Yung-Jue Bang (for clinical trials to the institution) from AstraZeneca, Novartis, Genentech/Roche, MSD, Merck Serano, Bayer, BMS, GSK, Pfizer, Eli Lilly, Boehringer-Ingelheim, MacroGenics, Boston Biomedical, FivePrime, Curis, Taiho, Takeda, Ono, Daiichi Sankyo, Astellas, BeiGene, Green Cross, CKD Pharma, Genexine. Martin Schuler (research grants provided to academic institution from AstraZeneca, Bristol-Myers Squibb, Novartis. Wan Teck Lim from Novartis (personal fees). Todd M. Bauer (to the institution) from Daiichi Sankyo, Medpacto (grants), Incyte (grants), Mirati Therapeutics (grants), MedImmune (grants), Abbvie (grants), AstraZeneca (grants), MabVax (grants), Stemline Therapeutics (grants), Merck (grants), Lilly (grants), GlaxoSmithKline (grants), Novartis (grants), Genentech (grants), Deciphera (grants), Merrimack (grants), Immunogen (grants), Millennium (grants), Phosplatin Therapeutics (grants), Calithera Biosciences (grants), Kolltan Pharmaceuticals (grants), Principia Biopharma (grants), Peloton (grants), Immunocore (grants), Roche (grants), Aileron Therapeutics (grants), Bristol-Myers Squibb (grants), Amgen (grants), Onyx (grants), Sanofi (grants), Boehringer-Ingelheim (grants), Astellas Pharma (grants), Five Prime Therapeutics (grants), Jacobio (grants), Top Alliance BioScience (grants), Janssen (grants), Clovis Oncology (grants), Takeda (grants), Karyopharm Therapeutics (grants), Foundation Medicine (grants), ARMO Biosciences (grants), Leap Therapeutics (grants and other), Ignyta (grants, non-financial support and other), Moderna Therapeutics (grants, non-financial support and other), Pfizer (grants, personal fees and other), Loxo (grants, personal fees and non-financial support), Bayer (grants, personal fees and non-financial support), Guardant Health (personal fees and non-financial support from) outside the submitted work. David Hong from Molecular Match

(Advisor), OncoResponse (founder), and Presagia Inc. (Advisor). Brigette Ma from Novartis (personal fees [advisory role] and research grant), BI (personal fees [advisory role]), BMS (personal fees [advisory role]), and MSD (personal fees [advisory role]), and Roche (personal fees [speaker]).

Other annual remuneration received:

- David Hong from LOXO, MiRNA, ASCO, AACR, SITC, and Genmab.
- Mikhail Akimov from Novartis.
- Samson Ghebremariam from Novartis.
- Monica Giovannini (self) from Novartis (employment).
- Monica Giovannini (family member) from Bluebirdbio (employment).

DATA AVAILABILITY STATEMENT

Novartis will not provide access to patient-level data if there is a reasonable likelihood that individual patients could be re-identified. Phase 1 studies, by their nature, present a high risk of patient re-identification; therefore, patient individual results for phase 1 studies cannot be shared. In addition, clinical data, in some cases, have been collected subject to contractual or consent provisions that prohibit transfer to third parties. Such restrictions may preclude granting access under these provisions. Where co-development agreements or other legal restrictions prevent companies from sharing particular data, companies will work with qualified requestors to provide summary information where possible.

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REFERENCES

1. Sierra JR, Tsao MS. c-MET as a potential therapeutic target and biomarker in cancer. *Ther Adv Med Oncol*. 2011;3(1 Suppl):S21-35.
2. Smolen GA, Sordella R, Muir B, et al. Amplification of MET may identify a subset of cancers with extreme sensitivity to the selective tyrosine kinase inhibitor PHA-665752. *Proc Natl Acad Sci USA*. 2006;103:2316-2321.
3. Bradley CA, Salto-Tellez M, Laurent-Puig P, et al. Targeting c-MET in gastrointestinal tumours: rationale, opportunities and challenges. *Nat Rev Clin Oncol*. 2017;14:562-576.
4. Sadiq AA, Salgia R. MET as a possible target for non-small-cell lung cancer. *J Clin Oncol*. 2013;31:1089-1096.
5. Cappuzzo F, Marchetti A, Skokan M, et al. Increased MET gene copy number negatively affects survival of surgically resected non-small-cell lung cancer patients. *J Clin Oncol*. 2009;27:1667-1674.
6. Kawakami H, Okamoto I, Okamoto W, Tanizaki J, Nakagawa K, Nishio K. Targeting MET amplification as a new oncogenic driver. *Cancers (Basel)*. 2014;6:1540-1552.
7. Schildhaus HU, Schultheis AM, Ruschoff J, et al. MET amplification status in therapy-naive adeno- and squamous cell carcinomas of the lung. *Clin Cancer Res*. 2015;21:907-915.
8. Bean J, Brennan C, Shih JY, et al. MET amplification occurs with or without T790M mutations in EGFR mutant lung tumors with acquired resistance to gefitinib or erlotinib. *Proc Natl Acad Sci USA*. 2007;104:20932-20937.
9. Chen HJ, Mok TS, Chen ZH, et al. Clinicopathologic and molecular features of epidermal growth factor receptor T790M mutation and c-MET amplification in tyrosine kinase inhibitor-resistant Chinese non-small cell lung cancer. *Pathol Oncol Res*. 2009;15:651-658.
10. Engelman JA, Zejnullahu K, Mitsudomi T, et al. MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. *Science*. 2007;316:1039-1043.
11. Sequist LV, Waltman BA, Dias-Santagata D, et al. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. *Sci Transl Med*. 2011;3:75ra26.
12. Yu HA, Arcila ME, Rekhtman N, et al. Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. *Clin Cancer Res*. 2013;19:2240-2247.
13. Minari R, Bordi P, Tiseo M. Third-generation epidermal growth factor receptor-tyrosine kinase inhibitors in T790M-positive non-small cell lung cancer: review on emerged mechanisms of resistance. *Transl Lung Cancer Res*. 2016;5:695-708.
14. Lorenzato A, Olivero M, Patane S, et al. Novel somatic mutations of the MET oncogene in human carcinoma metastases activating cell motility and invasion. *Cancer Res*. 2002;62:7025-7030.
15. Lee JH, Han SU, Cho H, et al. A novel germ line juxtamembrane Met mutation in human gastric cancer. *Oncogene*. 2000;19:4947-4953.
16. Drilon AE, Camidge DR, Ou S-HI, et al. Efficacy and safety of crizotinib in patients (pts) with advanced MET exon 14-altered non-small cell lung cancer (NSCLC). *J Clin Oncol*. 2016;34(15_suppl): 108.
17. Frampton GM, Ali SM, Rosenzweig M, et al. Activation of MET via diverse exon 14 splicing alterations occurs in multiple tumor types and confers clinical sensitivity to MET inhibitors. *Cancer Discov*. 2015;5:850-859.
18. Schrock AB, Frampton GM, Suh J, et al. Characterization of 298 patients with lung cancer harboring MET exon 14 skipping alterations. *J Thorac Oncol*. 2016;11:1493-1502.
19. Awad MM, Oxnard GR, Jackman DM, et al. MET exon 14 mutations in non-small-cell lung cancer are associated with advanced age and stage-dependent MET genomic amplification and c-Met overexpression. *J Clin Oncol*. 2016;34:721-730.
20. Liu X, Jia Y, Stoopler MB, et al. Next-generation sequencing of pulmonary sarcomatoid carcinoma reveals high frequency of actionable MET gene mutations. *J Clin Oncol*. 2016;34:794-802.
21. Raghav KP, Gonzalez-Angulo AM, Blumenschein GR Jr. Role of HGF/MET axis in resistance of lung cancer to contemporary management. *Transl Lung Cancer Res*. 2012;1:179-193.
22. Dimou A, Non L, Chae YK, Tester WJ, Syrigos KN. MET gene copy number predicts worse overall survival in patients with non-small cell lung cancer (NSCLC); a systematic review and meta-analysis. *PLoS ONE*. 2014;9:e107677.
23. Guo B, Cen H, Tan X, Liu W, Ke Q. Prognostic value of MET gene copy number and protein expression in patients with surgically resected non-small cell lung cancer: a meta-analysis of published literatures. *PLoS ONE*. 2014;9:e99399.
24. Awad MM, Leonardi GC, Kravets S, et al. Impact of MET inhibitors on survival among patients (pts) with MET exon 14 mutant (METdel14) non-small cell lung cancer (NSCLC). *J Clin Oncol*. 2017;35(15_suppl): 8511.
25. Lal B, Xia S, Abounader R, Laterra J. Targeting the c-Met pathway potentiates glioblastoma responses to gamma-radiation. *Clin Cancer Res*. 2005;11:4479-4486.
26. Akervall J, Guo X, Qian CN, et al. Genetic and expression profiles of squamous cell carcinoma of the head and neck correlate with cisplatin sensitivity and resistance in cell lines and patients. *Clin Cancer Res*. 2004;10:8204-8213.

27. Backes A, Zech B, Felber B, et al. Small-molecule. Part I: exceptions from the traditional pharmacophore approach of type I inhibition inhibitors binding to protein kinases. *Expert Opin Drug Discov*. 2008;3:1409-1425.
28. Gherardi E, Birchmeier W, Birchmeier C, Woude GV. Targeting MET in cancer: rationale and progress. *Nat Rev Cancer*. 2012;12:89-103.
29. Backes A, Zech B, Felber B, Klebl B, Müller G. Small-molecule inhibitors binding to protein kinase. Part II: the novel pharmacophore approach of type II and type III inhibition. *Expert Opin Drug Discov*. 2008;3(12):1427-1449.
30. Liu X, Wang Q, Yang G, et al. A novel kinase inhibitor, INCB28060, blocks c-MET-dependent signaling, neoplastic activities, and cross-talk with EGFR and HER-3. *Clin Cancer Res*. 2011;17:7127-7138.
31. Baltschukat S, Engstler BS, Huang A, et al. Capmatinib (INC280) is active against models of non-small cell lung cancer and other cancer types with defined mechanisms of *MET* activation. *Clin Cancer Res*. 2019;25:3164-3175.
32. Babb J, Rogatko A, Zacks S. Cancer phase I clinical trials: efficient dose escalation with overdose control. *Stat Med*. 1998;17:1103-1120.
33. Neuenschwander B, Branson M, Gsponer T. Critical aspects of the Bayesian approach to phase I cancer trials. *Stat Med*. 2008;27:2420-2439.
34. Esaki T, Hirai F, Makiyama A, et al. Phase I dose-escalation study of capmatinib (INC280) in Japanese patients with advanced solid tumors. *Cancer Sci*. 2019;110:1340-1351.
35. Hu X, Zheng X, Mo H, et al. P1.01-37 BPI-9016M, a novel c-Met inhibitor, in pretreated advanced solid tumor: results from a first-in-human, phase 1, dose-escalation study. *J Thorac Oncol*. 2018;13:S474.
36. Drilon A, Clark J, Weiss J, et al. OA12.02 Updated antitumor activity of crizotinib in patients with MET exon 14-altered advanced non-small cell lung cancer. *J Thorac Oncol*. 2018;13:S348.
37. Camidge DR, Otterson GA, Clark JW, et al. Crizotinib in patients (pts) with MET-amplified non-small cell lung cancer (NSCLC): updated safety and efficacy findings from a phase 1 trial. *J Clin Oncol*. 2018;36(15_suppl):9062-9062.
38. Felip E, Sakai H, Patel J, et al. OA12.01 Phase II data for the MET inhibitor tepotinib in patients with advanced NSCLC and MET exon 14-skipping mutations. *J Thorac Oncol*. 2018;13:S347.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Bang Y-J, Su W-C, Schuler M, et al. Phase 1 study of capmatinib in MET-positive solid tumor patients: Dose escalation and expansion of selected cohorts. *Cancer Sci*. 2020;111:536–547. https://doi.org/10.1111/cas.14254