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ORIGINAL REPORT

Phase Ib/II Study of Capmatinib (INC280) Plus Gefitinib After Failure of Epidermal Growth Factor Receptor (EGFR) Inhibitor Therapy in Patients With *EGFR*-Mutated, MET Factor–Dysregulated Non–Small-Cell Lung Cancer

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ABSTRACT

Purpose

Mesenchymal-epithelial transition factor (MET) dysregulation occurs in up to 26% of non–small-cell lung cancers (NSCLCs) after epidermal growth factor receptor (EGFR)–tyrosine kinase inhibitor (TKI) treatment. Capmatinib (INC280) is a potent and selective MET inhibitor with preclinical activity in combination with gefitinib in *EGFR*-mutant, *MET*-amplified/overexpressing models of acquired EGFR-TKI resistance. This phase Ib/II study investigated the safety and efficacy of capmatinib plus gefitinib in patients with *EGFR*-mutated, MET-dysregulated (amplified/overexpressing) NSCLC who experienced disease progression while receiving EGFR-TKI treatment.

Methods

Patients in phase Ib received capmatinib 100- to 800-mg capsules once per day or 200- to 600-mg capsules or tablets twice per day, plus gefitinib 250 mg once per day. Patients in phase II received the recommended phase II dose. The primary end point was the overall response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

Results

Sixty-one patients were treated in phase Ib, and 100 were treated in phase II. The recommended phase II dose was capmatinib 400 mg twice per day plus gefitinib 250 mg once per day. Preliminary clinical activity was observed, with an ORR across phase Ib/II of 27%. Increased activity was seen in patients with high *MET*-amplified tumors, with a phase II ORR of 47% in patients with a *MET* gene copy number ≥ 6. Across phases Ib and II, the most common drug-related adverse events were nausea (28%), peripheral edema (22%), decreased appetite (21%), and rash (20%); the most common drug-related grade 3/4 adverse events were increased amylase and lipase levels (both 6%). No significant drug-drug interactions between capmatinib and gefitinib were evident.

Conclusion

This study, focused on a predominant EGFR-TKI resistance mechanism in patients with *EGFR*-mutated NSCLC, shows that the combination of capmatinib with gefitinib is a promising treatment for patients with *EGFR*-mutated, MET-dysregulated NSCLC, particularly *MET*-amplified disease.

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INTRODUCTION

Dysregulation of the MET proto-oncogene receptor tyrosine kinase frequently occurs as a resistance mechanism to epidermal growth factor receptor (EGFR)–tyrosine kinase inhibitor (TKI) therapy. Patients with *EGFR*-mutated non–small-cell lung cancer (NSCLC) usually relapse within a year, despite high response rates to EGFR-TKIs.[1] MET dysregulation has been implicated as a therapeutically tractable resistance mechanism in a significant number of these patients, with *MET* amplification (activating ERBB3 signaling[2]) reported in 5% to 26% of NSCLCs with EGFR inhibitor resistance.[2-7]

Capmatinib (INC280) is a highly specific and potent MET inhibitor in biochemical and cellular assays that causes regression of MET-dependent (amplified/autocrine) tumors in animal models at well-tolerated doses.[8] Single-agent activity has been observed against *EGFR* wild-type tumor

ASSOCIATED CONTENT

Appendix
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models with strong *MET* amplification,[9] mutation,[10] and/or overexpression.[9] Capmatinib has also demonstrated preclinical activity in *EGFR*-mutant, MET-activated NSCLC when combined with first-generation[9] and third-generation (unpublished data) EGFR-TKIs. For example, the combination of capmatinib and gefitinib is active in *EGFR*-mutant/*MET*-amplified models of acquired EGFR inhibitor resistance.[9] Furthermore, capmatinib restores sensitivity to erlotinib and promotes apoptosis in NSCLC models rendered erlotinib-resistant by hepatocyte growth factor.[11]

Here, we report the results from a phase Ib/II study investigating the safety and efficacy of capmatinib in combination with gefitinib in patients with *EGFR*-mutated, MET-dysregulated (*MET*-amplified or MET-overexpressing) NSCLC who had experienced disease progression while receiving EGFR-TKI treatment.

METHODS

Study Oversight

This study was performed in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. The protocol was approved by the institutional review boards at each investigative site, and all patients provided written informed consent before any study procedures. The study was designed by the sponsor (Novartis Pharma AG, Basel, Switzerland).

Study Design

The phase Ib part of the study used an adaptive five-parameter Bayesian logistic regression model (BLRM)[12] guided by escalation with overdose control to determine the maximum tolerated dose (MTD) on the basis of dose-limiting toxicities (DLTs) recorded in cycle 1. With the introduction of a twice-per-day dosing schedule in addition to a once-per-day schedule, a second BLRM model was fitted with prior information on the basis of the once-per-day information. A tablet formulation was introduced after the capsule formulation to improve patient compliance and convenience, and an additional BLRM was used to assess safety and guide dose recommendations. The prior distributions for this model incorporated existing dose-toxicity data for single-agent capmatinib/gefitinib and the combination.

The primary objective was to determine the MTD and/or recommended phase II dose (RP2D) in phase Ib, and to estimate the overall response rate (ORR; per Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1) to capmatinib in combination with gefitinib in patients with MET-dysregulated NSCLC in phase II. Secondary objectives were to estimate time-dependent clinical activity of capmatinib plus gefitinib (overall survival, duration of response, and progression-free survival [PFS]), determine the safety and tolerability of capmatinib plus gefitinib, and characterize the pharmacokinetic (PK) profile. An exploratory objective was to study the pharmacodynamics (PD) of capmatinib plus gefitinib.

Patients

Overall eligibility criteria were age $\geq$ 18 years; Eastern Cooperative Oncology Group performance score $\leq$ 2; *EGFR*-mutant NSCLC (exon 19 deletion or L858R); acquired resistance to gefitinib, erlotinib, or afatinib treatment according to published acquired resistance criteria (documented clinical benefit as per RECIST and demonstrated progression while receiving continuous treatment or $\leq$ 30 days since EGFR-TKI administration)[13]; and demonstration of MET dysregulation. For phase Ib, patients were required to have *MET*-amplified tumors, defined as either *MET* gene copy number (GCN) $\geq$ 5 and/or a *MET*/centromere ratio of $\geq$ 2.0, or MET overexpression, defined as $\geq$ 50% of tumor cells with moderate or strong staining intensity. For phase II, patients were required to have experienced RECIST-recorded clinical benefit while taking a prior single-agent EGFR-TKI before progression. They were also required to be MET-dysregulated after disease progression while receiving an EGFR-TKI, which was initially defined as *MET* GCN $\geq$ 5 as determined by fluorescence in situ hybridization (FISH) or 50% of tumor cells with immunohistochemistry (IHC) 2+/3+, determined locally or centrally. In subsequent protocol amendments, these criteria were revised to 50% of tumor cells with IHC 3+ or IHC 2+ plus *MET* GCN $\geq$ 5 and then to 50% of tumor cells with IHC 3+ or *MET* GCN $\geq$ 4, determined centrally.

Patients with a known or documented *EGFR* T790M mutation were initially allowed (five patients, assessed centrally) but were later excluded through a protocol amendment. Other exclusion criteria included previous treatment with a MET inhibitor or hepatocyte growth factor–targeting therapy, receipt of more than two lines of chemotherapy and more than one line of EGFR-TKI therapy (gefitinib, erlotinib, or afatinib), and the presence of symptomatic CNS metastases that were neurologically unstable or required increasing doses of steroids.

Treatment Plan and Drug Administration

In phase Ib, patients were treated with gefitinib 250 mg once per day plus capmatinib capsules of either 100 to 800 mg once per day or 200 to 600 mg twice per day. The capmatinib tablet formulation was tested at 200 and 400 mg twice per day. In the phase II expansion, patients were treated with capmatinib at the RP2D of 400 mg twice per day (capsules or tablets) plus gefitinib 250 mg once per day. Full treatment and drug administration details together with statistical analysis of the primary objective (phase II) are provided in the Appendix (online only).

PK Analysis

Capmatinib and gefitinib concentrations were measured in plasma using liquid chromatography–tandem mass spectrometry. Noncompartmental PK analysis was performed to generate PK parameters of capmatinib and gefitinib, and the dose proportionality of capmatinib was assessed.

PD Biomarker Assessments

Paired pretreatment and post-treatment fresh tumor (and/or available archival tissue after disease progression while receiving an EGFR-TKI) samples were collected and evaluated for PD modulation of downstream components of the MET and EGFR signaling pathways. This exploratory analysis assessed key changes in the activation of downstream markers, including phosphorylated (*p*)-MET, *p*-ERK, *p*-AKT, and *p*-S6 (by IHC), to determine the level of pathway inhibition induced by the capmatinib and gefitinib combination. Potential correlative MET alteration markers of treatment efficacy were also evaluated; these included *MET* amplification (GCN as determined by FISH) and/or protein expression (as measured by IHC). Next-generation sequencing (Foundation Medicine, Cambridge, MA) was performed where tumor tissue was available, and any *MET* mutations were documented.

RESULTS

At the primary analysis cutoff date of June 10, 2016, enrollment was complete; 61 patients were enrolled in the phase Ib dose-escalation part, and 100 patients were enrolled in the phase II expansion (Table 1) from a total of 681 patients screened (Appendix Fig A1, online only). In phase Ib, gefitinib 250 mg once per day plus capmatinib capsules were evaluated at the following doses: 100 mg once per day (n = 5); 200 mg once per day (n = 7); 400 mg once per day (n = 6); 800 mg once per day (n = 7); 200 mg twice per day (n = 4); 400 mg twice per day (n = 12); and 600 mg twice per day (n = 5). Capmatinib in tablet formulation was evaluated at

Table 1. Patient Demographics and Disease Characteristics (full analysis set)

Characteristic	Phase Ib (n = 61)	Phase II (n = 100)	All (N = 161)
Median age (years)	58.0	61.0	60.0
Age group (years)			
< 65	46 (75)	62 (62)	108 (67)
≥ 65	15 (25)	38 (38)	53 (33)
Male	25 (41)	48 (48)	73 (45)
Race			
Asian	53 (87)	78 (78)	131 (81)
White	8 (13)	22 (22)	30 (19)
ECOG performance status			
0	12 (20)	17 (17)	29 (18)
1	45 (74)	81 (81)	126 (78)
2	4 (7)	2 (2)	6 (4)
Histology			
Adenocarcinoma	59 (97)	95 (95)	154 (96)
Adenosquamous cell carcinoma	0	2 (2)	2 (1)
Squamous cell carcinoma	0	2 (2)	2 (1)
Large cell carcinoma	1 (2)	0	1 (1)
Other	1 (2)	1 (1)	2 (1)
EGFR mutation status	n = 15	n = 47	n = 62
L858R	12 (80)	20 (43)	32 (52)
Exon 19 deletion	2 (13)	21 (45)	23 (37)
L858R + T790M	0 (0)	5 (11)	5 (8)
G719S/A/C	0 (0)	1 (2)	1 (2)
S768I	1 (7)	0 (0)	1 (2)
Prior lines of therapy			
One	27 (44)	59 (59)	86 (53)
Two or more	34 (56)	41 (41)	75 (47)
Prior EGFR-TKI	61 (100)	100 (100)	161 (100)
EGFR-TKI as last prior therapy			
Yes	43 (70)	84 (84)	127 (79)
Gefitinib	28 (46)	44 (44)	72 (45)
Erlotinib	14 (23)	34 (34)	48 (30)
Afatinib	1 (2)	5 (5)	6 (4)
Icotinib	0	1 (1)	2 (1)
No	18 (30)	16 (16)	34 (21)
Tumor MET status			
GCN < 4	ND	41 (41)	—
4 ≤ GCN < 6	ND	18 (18)	—
GCN ≥ 6	ND	36 (36)	—
IHC 0	ND	4 (4)	—
IHC 1+	ND	2 (2)	—
IHC 2+	ND	16 (16)	—
IHC 3+	ND	78 (78)	—

NOTE. All data are No. (%) unless otherwise stated. Molecular status was based on central assessment in all patients except one, who had a local IHC result only. A total of five patients had unknown or missing GCN.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; GCN, gene copy number; IHC, immunohistochemistry; MET, mesenchymal-epithelial transition factor; ND, not determined; TKI, tyrosine kinase inhibitor.

200 mg twice per day (n = 7) and 400 mg twice per day (subsequently declared as the RP2D; n = 8). The median duration of treatment exposure was 21.0 weeks (range, 1.0 to 975.0 weeks) from the start to the last treatment, per the data cutoff date. The overall median actual dose intensity of capmatinib was 791.6 mg/day (mean, 662.0 mg/day). In the 61 patients in phase Ib, the median and mean actual dose intensities of capmatinib (all doses) were 480.0 and 556.1 mg/day, respectively. In the 100 patients in phase II (with a planned dose of capmatinib 400 mg twice per day plus gefitinib 250 mg once per day), the median and mean actual dose intensities of capmatinib (tablet or capsule) were 796.3 and 726.6 mg/day, respectively. The median duration of follow-up was 12.2 months (from enrollment to last reported follow-up at the data cutoff date). At the time of data cutoff in phase Ib, 56 of 61 patients (92%) had discontinued treatment, most commonly because of disease progression (43 of 61 patients [70%]); five of 61 patients (8%) discontinued because of adverse events (AEs). At the time of data cutoff in phase II, 88 of 100 patients (88%) had discontinued treatment, most commonly because of disease progression (69 of 100 patients [69%]); 13 of 100 patients (13%) discontinued because of AEs.

Efficacy

Phase Ib efficacy. In phase Ib (n = 61), the ORR was 23% across all doses and regardless of MET status (Table 2). Four of eight evaluable patients treated at the RP2D of capmatinib 400 mg twice per day (tablets) plus gefitinib 250 mg once per day experienced a partial response (ORR, 50%); of these four responders,

Table 2. Best Overall Response by Dose Level (phase Ib) and by MET Amplification (GCN) and MET Overexpression (IHC) Status (phase II; full analysis set)

	Phase Ib, No. (%)					Phase II, No. (%)*								Phase Ib/II
Best Overall Response	100- to 800-mg Once-Per-Day Cap (n = 25)	200- to 600-mg Twice-Per-Day Cap (n = 21)	200-mg Twice-Per-Day Tab (n = 7)	400-mg Twice-Per-Day Tab (n = 8)	All (n = 61)	GCN < 4 (n = 41)	4 ≤ GCN < 6 (n = 18)	GCN ≥ 6 (n = 36)	IHC 0 (n = 4)	IHC 1+ (n = 2)	IHC 2+ (n = 16)	IHC 3+ (n = 78)	All (n = 100)	All (N = 161)
Complete response	0	0	0	0	**0**	0	0	0	0	0	0	0	**0**	**0**
Partial response	2 (8)	5 (24)	3 (43)	4 (50)	**14 (23)**	5 (12)	4 (22)	17 (47)	1 (25)	0	3 (19)	25 (32)	**29 (29)**	**43 (27)**
Stable disease	13 (52)	6 (29)	2 (29)	0	**21 (34)**	23 (56)	11 (61)	10 (28)	2 (50)	1 (50)	8 (50)	33 (42)	**44 (44)**	**65 (40)**
Progressive disease	8 (32)	6 (29)	2 (29)	2 (25)	**18 (30)**	7 (17)	2 (11)	5 (14)	1 (25)	1 (50)	3 (19)	11 (14)	**16 (16)**	**34 (21)**
Unknown†	2 (8)	4 (19)	0	2 (25)	**8 (13)**	6 (15)	1 (6)	4 (11)	0	0	2 (12)	9 (12)	**11 (11)**	**19 (12)**
Overall response rate	2 (8)	5 (24)	3 (43)	4 (50)	**14 (23)**	5 (12)	4 (22)	17 (47)	1 (25)	0	3 (19)	25 (32)	**29 (29)**	**43 (27)**
Disease control rate	15 (60)	11 (52)	5 (71)	4 (50)	**35 (57)**	28 (68)	15 (83)	27 (75)	3 (75)	1 (50)	11 (69)	58 (74)	**73 (73)**	**108 (67)**

NOTE. Bold type indicates data for all patients.
Abbreviations: Cap, capsule; GCN, gene copy number; IHC, immunohistochemistry; Tab, tablet.
*100 evaluable patients; GCN unknown for five patients.
†Patients had no valid postbaseline assessment (n = 18) or were assessed as having stable disease or non–complete response/non–progressive disease too early (≤ 6 weeks after study drug initiation; n = 1).

three had received an EGFR-TKI as their last prior therapy. The disease control rate (complete response, partial response, or stable disease) among all patients in phase Ib was 57% (Table 2).

Phase II efficacy. The ORR (primary end point; investigator assessment) was 29% (29 of 100 patients) regardless of MET status; of these responders, 25 of 29 (86%) had received an EGFR-TKI as their last prior therapy. The disease control rate was 73%; median duration of response was 5.6 months (95% CI, 3.8 to 7.2 months). In a subgroup analysis by *MET* GCN category, the best observed ORR was 47% in patients (n = 36) with *MET* GCN ≥ 6 tumors. In the MET overexpression status IHC 3+ subgroup, the ORR was 32% (25 of 78 patients; Table 2). A similar ORR of 31.8% (27 of 85 patients) was observed in the subgroup of patients with tumors of either IHC 3+ or IHC 2+ plus GCN ≥ 5.

Tumor reductions for individual patients by GCN and IHC subgroup, as best percentage change from baseline in the sum of tumor lesion diameters, are presented in Figure 1. Baseline tumor molecular status (FISH GCN) by treatment group and according to IHC protein expression status are listed in Table 1 and Appendix Table A1 (online only). Median PFS in the GCN ≥ 6 (n = 36) and IHC 3+ (n = 78) subgroups was 5.49 months (95% CI, 4.21 to 7.29 months) and 5.45 months (95% CI, 3.71 to 7.10 months), respectively; full PFS data are provided in the Appendix.

Safety

One of five DLT-evaluable patients treated with 800-mg once-per-day capsules experienced a DLT of grade 3 dizziness. The single evaluable patient treated with 600-mg twice-per-day capsules experienced two DLTs of grade 4 cough and grade 4 dyspnea. There were no DLTs reported in 10 patients treated with capsules or the seven patients treated with tablets at the 400-mg twice-per-day dose level. The RP2D was declared as capmatinib tablet 400 mg twice per day plus gefitinib 250 mg once per day.

All-grade and grade 3/4 AEs, regardless of study drug relationship, are listed in Table 3. A total of 140 of 161 patients (87%) reported at least one AE believed to be related to study treatment, most frequently (≥ 20% of patients) nausea (28%), peripheral edema (22%), decreased appetite (21%), and rash (20%). Grade 3/4 AEs believed to be study drug related were reported in 46 of 161 patients (29%); the most common (≥ 5% of patients) were increased amylase and lipase levels (both 6%). Serious AEs were reported in 53 of 161 patients (33%) overall, with 11 of 161 (7%) believed to be study drug related. Overall, 27 of 161 patients (17%) reported AEs that led to study drug discontinuation, and 71 of 161 patients (44%) reported AEs requiring dose adjustment or interruption. Analysis of the capsule- and tablet-treated subgroups in phase II revealed that slightly fewer patients in the capsule group experienced AEs (96% *v* 100%). A total of 85 of 161 patients (53%) died (47 patients in phase II, of whom 34 were in the capsule group and 13 were in the tablet group); 13 of 161 patients (8%) died during the study (up to 30 days after the end of treatment), primarily (10 of 13 [77%]) as a result of the study indication. One patient each (< 1%) died as a result of dyspnea, myocardial infarction, and pneumonia—of these, only the dyspnea was believed to be related to the study treatment; in this patient, neither pneumonitis nor infection were diagnosed. Dyspnea occurred in only 2% of patients overall, with no instances of dyspnea reported in phase II.

PK Analysis

Capmatinib was rapidly absorbed after oral administration with gefitinib, with the tablet formulation providing higher mean exposures than the capsule at the same dose levels tested. Full PK results are listed in Appendix Table A2 (online only). The mean plasma concentration versus time profiles on cycle 1 day 15 (C1D15) for the capmatinib twice-per-day regimens by dose level and formulation are provided in Figure 2. No significant drug-drug interactions between capmatinib and gefitinib were observed. Compared with single-agent capmatinib (RP2D), mean steady-state exposure (area under the plasma concentration–time curve ranging from 0 to 12 hours and maximum plasma concentration) was higher (1.34-fold and 1.30-fold, respectively) with gefitinib coadministration (unpublished data). Mean plasma exposures to gefitinib were comparable among treatments at various doses with different dose regimens or formulations of capmatinib and were in the range of exposures reported for single-agent treatment.[14]

PD Analysis

Exploratory analyses of baseline and C1D15 tumor biopsy MET H-scores were performed with samples from five patients treated with 400-mg twice-per-day capsules (phase Ib/II patients with noncompulsory screening/C1D15 p-MET staining intensity [H-score] data). Significant MET pathway inhibition was induced in these patients, with p-MET H-score reductions of 15 to 260 in four of the five patients (Fig 3).

DISCUSSION

The RP2D for capmatinib in combination with gefitinib 250 mg once per day was declared as 400-mg twice-per-day tablets on the basis of a combination of safety, PK, and PD data. Preliminary clinical activity was observed in patients treated with the combination, with an ORR of 27% for all patients across phase Ib and II, and an ORR of 29% for phase II patients treated at the RP2D. In phase II, 86% of responding patients had received an EGFR-TKI as their last prior therapy; therefore, few patients had received intervening chemotherapy, and potential retreatment effects were not considered to affect the ORR. Notable activity was seen in patients with high *MET*-amplified tumors. In a post hoc subgroup analysis by *MET* GCN category, the best observed ORR was 47% in phase II patients with MET GCN ≥ 6 tumors; the ORR was 32% in patients with IHC 3+ tumors, which was comparable with that observed in patients with IHC 2+ plus GCN ≥ 5 tumors. Thus IHC 3+ status was predictive of response, whereas IHC 0 to 2+ was not predictive unless combined with amplification status, although patient numbers in the IHC 0 to 1+ categories were small. Additional studies are required to provide conclusive validation of IHC-measured MET expression as a predictive biomarker. Of note, expression of MET may not always accurately reflect MET receptor activation.[15,16] However, it is yet to be established whether activated p-MET may be a more accurate indicator of MET activation than total MET expression by IHC. Overall, the exploratory

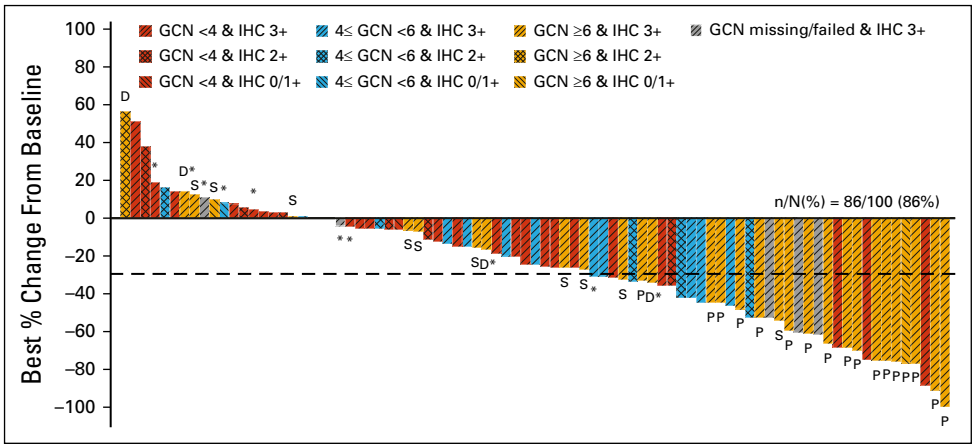

Fig 1. Best percentage change in sum of diameters of target lesions in all phase II patients by gene copy number (GCN) and immunohistochemistry (IHC) subgroup (full analysis set). N represents the number of patients with a baseline and at least one post-baseline assessment of tumor lesions (investigator assessment). D, progression of disease; P, partial response; S, stable disease. (*) Percentage change in sum of diameters of target lesion contradicted by overall lesion response of progressive disease.

biomarker data generated in this study indicate that MET detection by FISH using a cutoff value of GCN ≥ 6, compared with MET staining by IHC, more accurately identifies the patient population most likely to respond to the combination of capmatinib plus gefitinib.

Although *MET* GCN was used to define MET positivity in this study, other FISH-based methods have been used. *MET/CEP7* ratio can be used to distinguish true amplification and polysomy,[17] and a ratio of ≥ 2 is considered an equivalent positive threshold.[16] However, in initial analyses of patient samples in this study (unpublished data), responses better correlated with GCN versus *MET/CEP7* ratio, and on the basis of these data, GCN was selected as the biomarker.

Other recent advanced-stage studies employing different biomarker selection criteria have not provided positive data. A phase II study of the MET-directed monoclonal antibody onartuzumab plus erlotinib showed improved outcomes in patients who were MET positive by IHC, but a subsequent phase III study was negative.[18,19] A phase III study of tivantinib was stopped early because of an increased incidence of interstitial lung disease; the study also failed to demonstrate any improvement in PFS or overall survival.[20] However, alternative mechanisms of action have been suggested for tivantinib.[21] A study of tepotinib plus gefitinib in patients who experienced disease progression while receiving EGFR-TKI therapy provided an ORR of 28% for patients with IHC 3+ tumors, and the data suggested an increased likelihood of disease stabilization in patients with IHC 2+ tumors.[22] A subsequent phase II study may shed more light on the utility of IHC as a biomarker for MET inhibitor therapy. A phase I study of crizotinib and dacomitinib in the same patient population did not

Table 3. Adverse Events, Regardless of Causality (any grade occurring in ≥ 10% of patients; safety set)

	Phase Ib (n = 61)		Phase II (n = 100)		All Patients (N = 161)	
Adverse Event Preferred Term	All Grades	Grades 3/4	All Grades	Grades 3/4	All Grades	Grades 3/4
Total	61 (100)	35 (57)	98 (98)	56 (56)	159 (99)	91 (57)
Nausea	25 (41)	2 (3)	33 (33)	5 (5)	58 (36)	7 (4)
Decreased appetite	21 (34)	1 (2)	31 (31)	3 (3)	52 (32)	4 (2)
Peripheral edema	15 (25)	1 (2)	34 (34)	5 (5)	49 (30)	6 (4)
Hypoalbuminemia	13 (21)	0	33 (33)	1 (1)	46 (29)	1 (1)
Vomiting	23 (38)	3 (5)	21 (21)	3 (3)	44 (27)	6 (4)
Rash	18 (30)	1 (2)	21 (21)	2 (2)	39 (24)	3 (2)
Diarrhea	16 (26)	1 (2)	22 (22)	1 (1)	38 (24)	2 (1)
Fatigue	10 (16)	0	25 (25)	6 (6)	35 (22)	6 (4)
Paronychia	16 (26)	0	17 (17)	1 (1)	33 (20)	1 (1)
Cough	11 (18)	1 (2)	20 (20)	0	31 (19)	1 (1)
Increased amylase	11 (18)	5 (8)	18 (18)	6 (6)	29 (18)	11 (7)
Dyspnea	17 (28)	6 (10)	11 (11)	3 (3)	28 (17)	9 (6)
Anemia	5 (8)	2 (3)	21 (21)	2 (2)	26 (16)	4 (2)
Increased blood creatinine	6 (10)	0	17 (17)	0	23 (14)	0
Constipation	8 (13)	0	14 (14)	0	22 (14)	0
Increased ALT	6 (10)	1 (2)	15 (15)	2 (2)	21 (13)	3 (2)
Increased lipase	5 (8)	4 (7)	15 (15)	6 (6)	20 (12)	10 (6)
Increased AST	4 (7)	1 (2)	15 (15)	2 (2)	19 (12)	3 (2)
Dizziness	9 (15)	2 (3)	9 (9)	1 (1)	18 (11)	3 (2)
Increased blood bilirubin	5 (8)	0	12 (12)	1 (1)	17 (11)	1 (1)
Hemoptysis	7 (11)	0	10 (10)	1 (1)	17 (11)	1 (1)
Insomnia	8 (13)	0	9 (9)	0	17 (11)	0

NOTE. Data are given as No. (%).

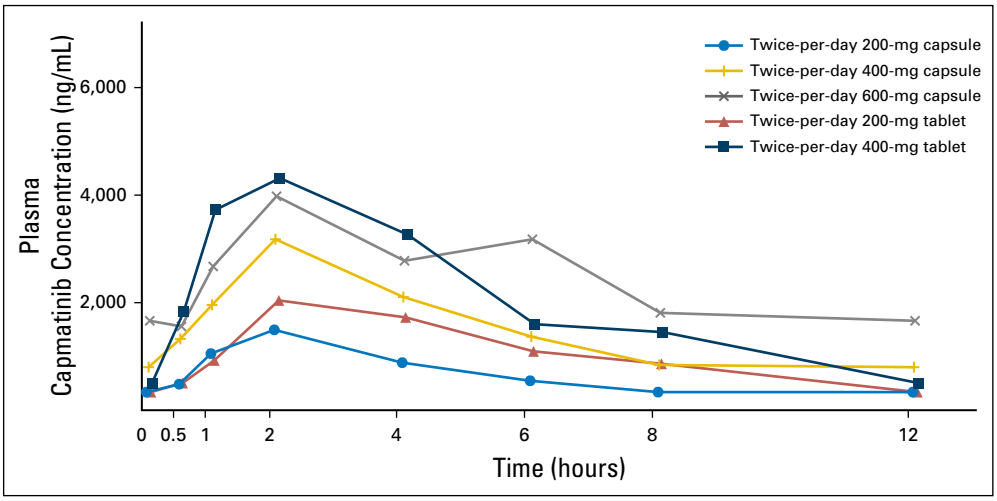

Fig 2. Mean plasma concentration-time curves on cycle 1 day 15 for capmatinib twice-per-day regimens by dose level and formulation (full capmatinib pharmacokinetic analysis set). Zero concentrations at individual timepoints are excluded from geometric mean computation. Concentration at 12 h after dose is carried forward from the predose value (based on assumption of steady state).

select patients on the basis of MET status and provided limited activity (one partial response; 46% with stable disease), with no association observed between biomarker expression and clinical activity.[23] This combination was also associated with unacceptable increased toxicity.[23] A phase I study of the combination of crizotinib and erlotinib also provided limited activity (ORR, 8%) in patients with *EGFR*-mutant NSCLC, albeit in a largely unselected patient population. Furthermore, the MTD of the combination was below the approved dose of either agent, and a phase II study was not initiated.[24]

In contrast to a number of other combination studies, capmatinib in combination with gefitinib is tolerable. The most common study drug–related any-grade and grade 3/4 AEs were nausea and increased lipase or amylase levels, respectively.

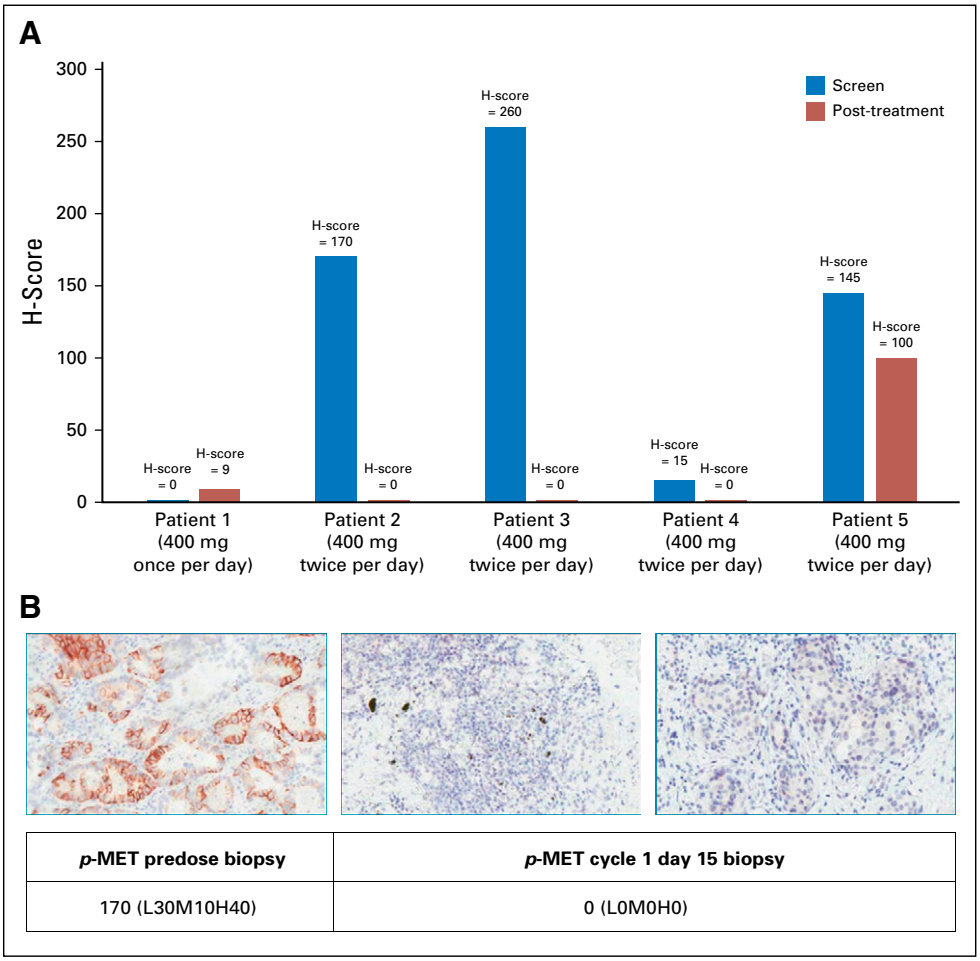

Fig 3. (A) Mesenchymal-epithelial transition factor (MET) H-score (phosphorylated-MET [*p*-MET]) at baseline and post-treatment (cycle 1 day 15). (B) Example pharmacodynamic analysis of *p*-MET in paired predose and postdose (cycle 1 day 15) biopsy immunohistochemistry analysis in one patient treated at the recommended phase II dose of capmatinib 400 mg twice per day plus gefitinib 250 mg once per day, using the *p*-MET cell signaling antibody 3077. Immunohistochemistry images previously presented (ASCO, 2014) and used with permission of the presenter (Y.-L.W.).

Peripheral edema believed to be drug related occurred in 22% of patients; this has been reported for other MET inhibitors[25,26] and may be a potential drug class effect not specific to capmatinib. Although slightly fewer patients in the capsule group compared with the tablet group experienced AEs (96% *v* 100%) in phase II, there were racial differences between the groups, with the capsule group comprising Chinese patients only, whereas approximately half of the patients in the tablet group were Asian patients from other countries. Overall, capmatinib 400-mg twice-per-day tablets were associated with a tolerability and safety pro-file comparable to that seen with capsules. No significant drug-drug interactions were reported between capmatinib and gefitinib.

On the basis of the PD data from this study, the declared RP2D of capmatinib tablet 400 mg twice per day plus gefitinib 250 mg once per day seemed to be sufficient to completely shut down the MET pathway. Exploratory (five of 161 patients) predose and postdose paired-biopsy analysis of MET phosphorylation by IHC revealed significant MET pathway inhibition after treatment with capmatinib 400-mg twice-per-day capsules in four of the five patients. An association between these markers and clinical outcome, therefore, warrants additional investigation.

This was the first phase II study to focus on the second most predominant resistance mechanism (after T790M mutation) to EGFR-TKI therapy in patients with *EGFR*-mutated NSCLC, for which limited treatment options are currently available. The combination of capmatinib with gefitinib has been shown to be both feasible and rational, and the data from this study suggest that the combination of capmatinib with an EGFR-TKI may be a promising treatment option for patients with *EGFR*-mutated, MET-dysregulated NSCLC and particularly for patients with *MET*-amplified tumors.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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Phase Ib/II Study of Capmatinib (INC280) Plus Gefitinib After Failure of Epidermal Growth Factor Receptor (EGFR) Inhibitor Therapy in Patients With *EGFR*-Mutated, MET Factor–Dysregulated Non–Small-Cell Lung Cancer

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Appendix

Treatment Plan and Drug Administration

Patients were dosed continuously in 28-day cycles, and treatment continued until disease progression (Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1; investigator assessed), unacceptable toxicity precluding additional treatment, pregnancy, discontinuation at the discretion of the investigator or patient, withdrawal of consent, loss to follow-up, or death. Tumor lesions were assessed (RECIST version 1.1; investigator confirmed) using computed tomography unless contraindicated, in which case magnetic resonance imaging with contrast was performed. Efficacy imaging assessments were carried out at screening, every two cycles, 4 weeks after any reported response, and at the end of treatment (if no scan $\leq$ 30 days before the end of treatment). Safety assessments were performed on the basis of all adverse events assessed according to Common Terminology Criteria for Adverse Events version 4.0, clinical laboratory data, and physical examinations.

Statistical Analysis of the Primary Objective (phase II)

For the primary analysis, the overall response rate (ORR) was estimated using a Bayesian approach with a minimally informative beta prior distribution. However, the ORR estimate on the basis of the frequency of complete or partial responses is presented; results were almost identical.

On the basis of the posterior distribution, the probability that the true ORR lies in the following categories was calculated: unacceptable efficacy: 0%, 5%; limited efficacy: 5%, 20%; clinically relevant efficacy, 20%, 100%. The criterion for evidence of clinically relevant efficacy of the combination was an observed ORR of $\geq$ 20% and a posterior risk of $<$ 2.5% that the true ORR was in the unacceptable efficacy category.

Progression-Free Survival

In 100 evaluable patients treated at the recommended phase II dose (mesenchymal-epithelial transition factor [MET] positivity initially defined as *MET* gene copy number [GCN] $\geq$ 5 or 50% of tumor cells with immunohistochemistry [IHC] 2+/3+, revised to 50% of tumor cells with IHC 3+ or IHC 2+ plus *MET* GCN $\geq$ 5, and then to 50% of tumor cells with IHC 3+ or *MET* GCN $\geq$ 4), the median progression-free survival (PFS; secondary end point) for all patients was 5.5 months (95% CI, 3.8 to 5.6 months). Median PFS in the GCN $\geq$ 6 (n = 36), 4 $\leq$ GCN $<$ 6 (n = 18), and GCN $<$ 4 (n = 41) subgroups was 5.49 months (95% CI, 4.21 to 7.29 months), 5.39 months (95% CI, 3.65 to 7.46 months), and 3.91 months (95% CI, 3.65 to 5.55 months), respectively (Appendix Fig A2A, online only). Median PFS in the IHC 3+ (n = 78) and IHC 2+/GCN $\geq$ 5 (n = 8) subgroups was 5.45 months (95% CI, 3.71 to 7.10 months) and 7.29 months (95% CI, 1.81 to 9.07 months), respectively (Appendix Fig A2B).

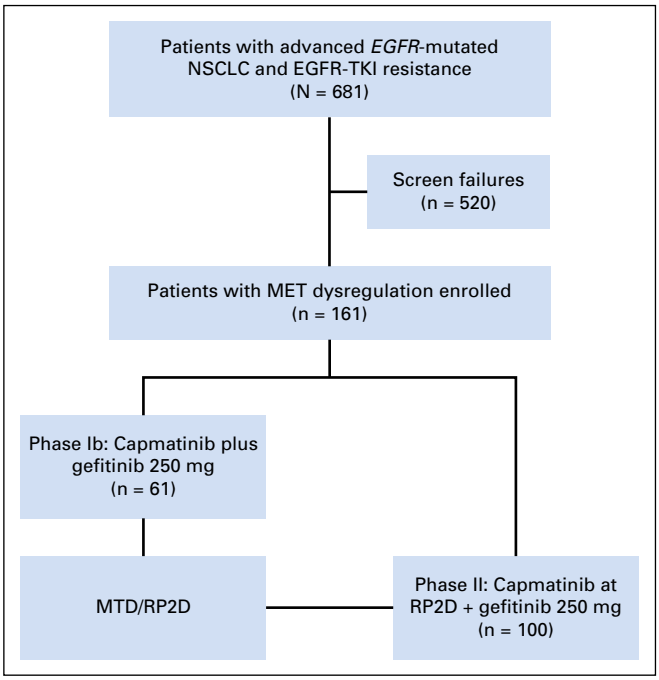

Fig A1. CONSORT diagram. MET, mesenchymal-epithelial transition factor; MTD, maximum tolerated dose; NSCLC, non–small-cell lung cancer; RP2D, recommended phase II dose; TKI, tyrosine kinase inhibitor.

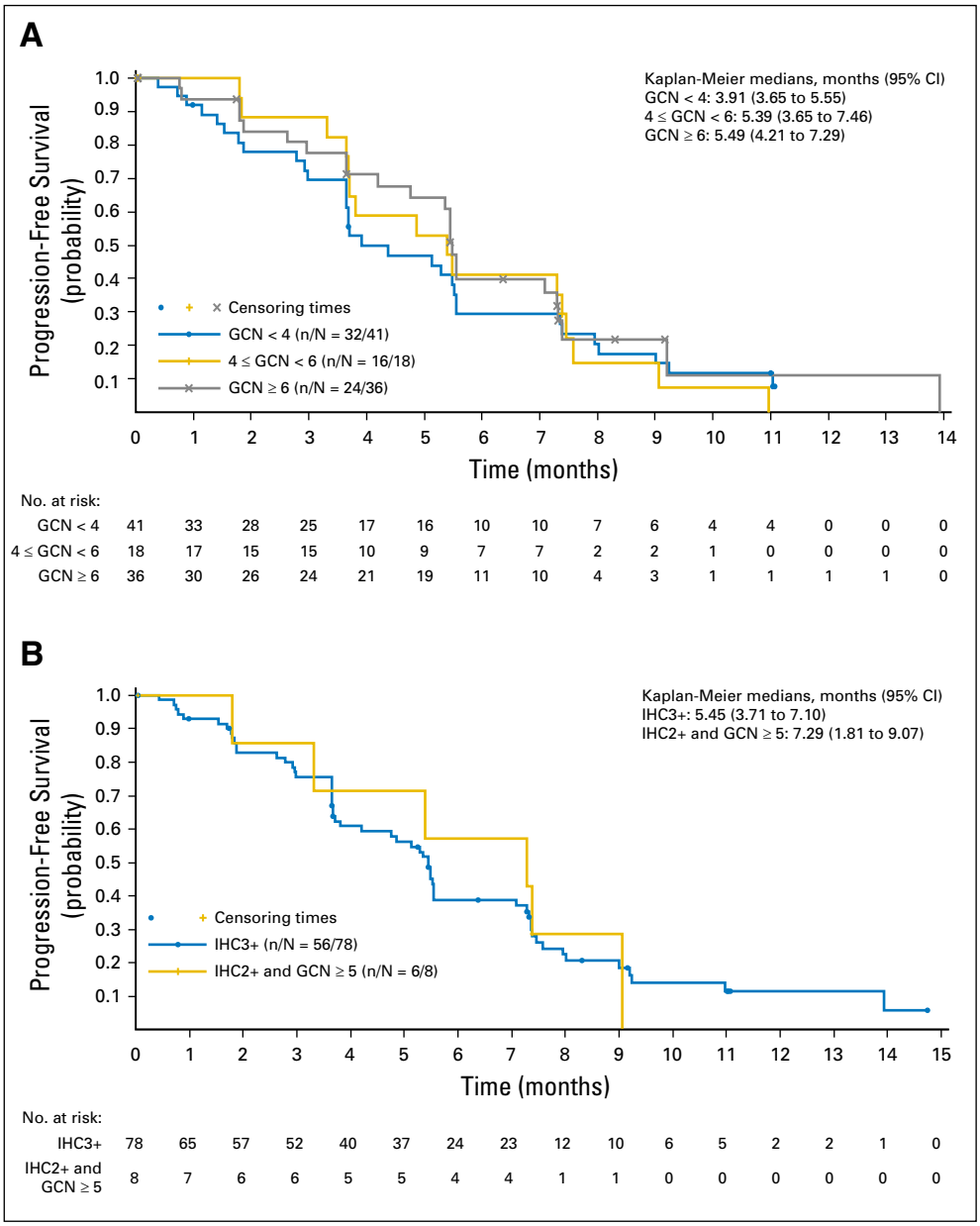

Fig A2. (A) Kaplan-Meier plot of progression-free survival for patients treated in the phase II part by gene copy number (GCN) subgroup (full analysis set). (B) Kaplan-Meier plot of progression-free survival for patients treated in the phase II part by GCN subgroup (full analysis set). IHC, immunohistochemistry.

Table A1. Tumor Molecular Status at Baseline for All Phase II Patients (N = 100; full analysis set)

IHC Score	GCN < 4	4 ≤ GCN < 6	GCN ≥ 6	Missing/Unknown	Total
0	0	2 (2)	2 (2)	0	4 (4)
1+	2 (2)	0	0	0	2 (2)
2+	8 (8)	6 (6)	2 (2)	0	16 (16)
3+	31 (31)	10 (10)	32 (32)	5 (5)	78 (78)
Missing/unknown	0	0	0	0	0
Total	41 (41)	18 (18)	36 (36)	5 (5)	100 (100)

NOTE. Data are given as No. (%). Molecular status was based on central assessment in all patients except one, who had a local IHC result only.
Abbreviations: GCN, gene copy number; IHC, immunohistochemistry.

Table A2. Summary of PK Parameters for Capmatinib Tablets or Capsules on Cycle 1 Day 15 in Phase Ib (PK analysis set)

	Once per Day				Twice per Day				
PK Parameter	100-mg Cap (n = 4)	200-mg Cap (n = 7)	400-mg Cap (n = 6)	800-mg Cap (n = 4)	200-mg Cap (n = 4)	400-mg Cap (n = 10)	600-mg Cap (n = 2)	200-mg Tab (n = 7)	400-mg Tab (n = 7)
$AUC_{0\text{-}12\ h}$, ng*h/mL	n = 4	n = 7	n = 5	n = 3	n = 4	n = 10	n = 2	n = 7	n = 7
Geomean	4,130	7,830	26,900	23,600	8,420	19,400	34,800	13,400	28,200
CV%	54.6	65.4	50.0	126.6	66.9	57.3	56.8	29.4	20.6
C_{max}, ng/mL	n = 4	n = 7	n = 6	n = 4	n = 4	n = 10	n = 2	n = 7	n = 7
Geomean	701	1,020	3,150	4,800	1,740	3,740	4,630	2,470	6,560
CV%	75.6	121.3	188.4	149.9	63.1	57.6	44.3	27.2	27.0
T_{max} (hours)	n = 4	n = 7	n = 6	n = 4	n = 4	n = 10	n = 2	n = 7	n = 7
Median	1.96	2.00	2.00	2.05	1.50	2.00	5.00	2.00	1.08
Range	1.50-3.92	1.00-24.0	1.98-6.00	1.92-5.97	1.00-3.98	0.50-4.00	4.00-6.00	1.00-4.00	1.00-4.00
$T_{1/2}$ (hours)	n = 4	n = 6	n = 5	n = 3	n = 3	n = 9	—	n = 7	n = 6
Geomean	3.83	4.82	3.14	3.60	3.09	2.81	—	3.37	3.08
CV%	14.5	37.1	11.4	23.6	33.3	38.6	—	52.5	27.3

NOTE. During phase Ib dose escalation, predose and 0.5, 1.0, 2.0, 4.0, 6.0, 8.0 (all cohorts), and 24-hour (once-per-day–dosing cohorts only) postdose blood samples were collected on cycle 1 day 15 for PK analysis; predose samples were collected on cycle 2 days 1 and 15, and cycles 3 and 4 day 1. During phase II, sparse samples were collected predose and 2 and 6 hours after dose on cycle 1 day 15; predose samples were also collected on cycle 2 days 1 and 15, and cycles 3 and 4 day 1. Capmatinib was rapidly absorbed after oral administration with gefitinib, with the median time to peak plasma concentrations generally ranging from 1 to 2 hours. The steady-state AUC_{tau} and C_{max} of capmatinib capsules were generally dose proportional across the dose range for once-per-day (100 to 800 mg) and twice-per-day (200 to 600 mg) administration, although the geomean AUC_{tau} did not increase with increasing dose (400 to 800 mg once per day). The estimated geomean $T_{1/2}$ ranged from 2.8 to 4.8 hours across the dose range and with different dose regimens or formulations. The tablet formulation provided higher mean exposures than the capsule at the same dose levels tested. The geomean steady-state exposure of capmatinib at the RP2D (400-mg twice-per-day tablet) was 28,200 ng*h/mL (CV, 20.6%) for $AUC_{0-12\ h}$ and 6,560 ng/mL (CV, 27.0%) for C_{max} (n=7).
Abbreviations: AUC, area under the plasma concentration–time curve; Cap, capsule; C_{max}, maximum plasma concentration; CV, coefficient of variation; geomean, geometric mean; PK, pharmacokinetic; RP2D, recommended phase II dose; $T_{1/2}$, half-life; Tab, tablet; T_{max}, time to peak plasma concentration.