Phase I/II Study of Capmatinib Plus Erlotinib in Patients With MET-Positive Non–Small-Cell Lung Cancer

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PURPOSE MET dysregulation is an oncogenic driver in non–small-cell lung cancer (NSCLC), as well as a mechanism of TKI (tyrosine kinase inhibitor) resistance in patients with epidermal growth factor receptor (EGFR)–mutated disease. This study was conducted to determine safety and preliminary efficacy of the combination EGFR and MET inhibitors as a strategy to overcome and/or delay EGFR-TKI resistance.

METHODS A standard 3 + 3 dose-escalation trial of capmatinib in combination with erlotinib in patients with MET-positive NSCLC was used. Eighteen patients in the dose-escalation cohort received 100-600 mg twice daily of capmatinib with 100-150 mg daily of erlotinib. There were two dose-expansion cohorts. Cohort A included 12 patients with EGFR-mutant tumors resistant to TKIs. Cohort B included five patients with EGFR wild-type tumors. The primary outcome was to assess safety and determine the recommended phase II dose (RP2D) of the combination.

RESULTS The most common adverse events of any grade were rash (62.9%), fatigue (51%), and nausea (45.7%). Capmatinib exhibited nonlinear pharmacokinetics combined with erlotinib, while showing no significant drug interactions. The RP2D was 400 mg twice daily capmatinib tablets with 150 mg daily erlotinib. The overall response rate (ORR) and DCR in dose-expansion cohort A was 50% and 50%, respectively. In cohort B, the ORR and disease control rate were 75% and 75%.

CONCLUSION Capmatinib in combination with erlotinib demonstrated safety profiles consistent with prior studies. We observed efficacy in specific patient populations. Continued evaluation of capmatinib plus EGFR-TKIs is warranted in patients with EGFR activating mutations.

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INTRODUCTION

Aberrant MET signaling plays a role in tumor invasion, progression, metastasis, and survival.\(^1\)\(^-\)\(^5\) MET amplification is a well-established mechanism of resistance to first-generation EGFR-TKIs, occurring in 5%-22% of patients with EGFR-mutated non–small-cell lung cancer (NSCLC).\(^6\)\(^-\)\(^8\) In addition, MET amplification is a common resistance mechanism after treatment with the third-generation EGFR TKI osimertinib, ranging in frequency from 14% to 30%.\(^9\)\(^-\)\(^12\) De novo MET amplification and MET exon 14 splicing mutations are known independent oncogenic drivers.\(^4\)\(^,\)\(^13\)\(^,\)\(^14\) Preclinically, MET protein overexpression has been shown to be oncogenic, but its transformative potential in human tumors is controversial.\(^15\)\(^,\)\(^16\) Overall, MET dysregulation plays a significant biologic role in lung cancer, making it an ideal drug target.

Several MET inhibitors have been evaluated in patients with lung cancer. Early studies evaluated onartuzumab (an anti-MET monoclonal antibody) in combination with erlotinib in recurrent NSCLC.\(^16\)\(^,\)\(^17\) In the phase II study, patients with MET 2+ or 3+ by immunohistochemistry (IHC) demonstrated a significant improvement in survival end points compared with low MET expression. Despite this, the phase III trial was negative.\(^18\) Tivantinib, a non-ATP competitive small molecule MET inhibitor, was evaluated in combination with erlotinib in a phase II trial of unselected pretreated patients. The combination did not meet its overall efficacy goal; however, a planned subset analysis showed a trend toward prolonged progression-free survival (PFS) in patients with MET amplification.\(^19\) This lack of efficacy may be due to the lack of specificity of tivantinib for the MET pathway compared with other MET inhibitors.\(^20\)

Capmatinib (INC280) is a highly potent and selective oral MET inhibitor that has recently been approved for the treatment of tumors with MET exon 14 mutations.\(^21\) In the phase I study, antitumor activity was observed in pretreated patients with EGFR wild-type (WT) tumors with MET dysregulation. The most frequent adverse
Key Objective
Aberrant MET signaling plays a role in tumor invasion, progression, metastasis, and survival in non–small-cell lung cancer. It is a common resistance mechanism to third-generation EGFR TKIs, and MET amplification and exon 14 mutations are independent oncogenic drivers. Because of overlapping signaling pathways, we sought to determine whether the combination of capmatinib with erlotinib would be safe and demonstrate an efficacy signal in patients with EGFR- or MET-altered tumors.

Knowledge Generated
We demonstrated that the combination of capmatinib and erlotinib is safe. Furthermore, we demonstrated an overall response rate of 50% in patient with EGFR mutations and acquired resistance to EGFR TKIs and further demonstrated the efficacy of capmatinib in patients with MET exon 14 mutations.

Relevance
The use of combination targeted therapy, capmatinib, and EGFR TKI may help to treat patients with resistance to frontline therapy and is important to consider as frontline therapy to provide prolonged responses.

METHODS
This trial was conducted at the University of California, Davis (UCD) and the University of California, San Francisco (UCSF). A standard 3 + 3 dose-escalation design was used, as illustrated in Figure 1. The initial phase of the study was a dose escalation to determine the maximum tolerated dose (MTD) of capmatinib plus erlotinib; there was no intra-patient dose escalation. This was followed by two expansion cohorts; cohort A consisted of patients with EGFR-mutated tumors resistant to erlotinib, and cohort B enrolled erlotinib-naive patients with WT EGFR tumors. Cohort B was designed based on preclinical and clinical data indicating that MET alterations serve as an oncogenic driver in a subset of patients with WT EGFR tumors.17,19 While the study was ongoing, MET exon 14 mutations emerged as a predictive marker for TKI response, and additional studies clarified the role of MET alterations as oncogenic drivers.18,24-26 Because of slowed enrollment resulting from changes in standard-of-care treatment in the EGFR-mutated population and the US Food and Drug Administration withdrawal of erlotinib in the EGFR WT population, the study was terminated before enrollment was completed in cohort B.

This study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization harmonized Tripartite Guidelines for good clinical practice, and US 21 code of federal regulations. Site-specific institutional review boards approved the study protocol and amendments. All patients provided written informed consent. The study is registered at www.ClinicalTrials.gov (ClinicalTrials.gov identifier: NCT01911507).

![Figure 1. Consort diagram of clinical trial. EGFR, epidermal growth factor receptor; RP2D, recommended phase II dose; TKI, tyrosine kinase inhibitor.](image-url)
Patients
Key eligibility criteria included advanced/metastatic NSCLC with measurable disease, age ≥ 18 years, Eastern Cooperative Oncology Group performance status (ECOG PS) 0-2, MET increased copy number by fluorescence in situ hybridization (FISH; CNG or MET/CEN7 ratio outside of normal range), MET IHC 2-3+, positive reverse transcriptase polymerase chain reaction (RT-PCR) value, or an exon 14 splice site mutation (Data Supplement). Patients in cohort A must have an EGFR activating mutation and a biopsy at the time of progression that shows evidence of MET positivity.

Treatment
Capmatinib capsules were administered orally every 12 hours of a 28-day cycle at 100-600 mg. Dose level 6 was used to determine whether tablets demonstrated a similar safety profile as capsules. The expansion cohort was based on information provided by the sponsor that 400-mg tablets demonstrated equivalent pharmacokinetics (PK) to 600-mg capsules. In addition, the capsule formulation required patients to take up to eight capsules twice daily. For these reasons, the formulation was shifted to tablets during the study. Erlotinib was administered at 100 mg orally once daily in dose level 1 and escalated to 150 mg orally daily in dose levels 2-6. Dose modifications were made independently for each drug on the basis of specific toxicities, and treatment was administered as per study protocol (Data Supplement).

Assessments
Adverse events (AEs) were assessed for severity using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE version 4.0).

In dose escalation, all evaluable patients were included in the dose-escalation decisions except for patient 15 (dose level 5), who discontinued the study after 2 days and was not replaced because of the opening of dose level 6, a pharmacologically equivalent dose. A dose-limiting toxicity (DLT) was defined as per the study protocol (Data Supplement).

PK blood samples were collected for patients in the dose-escalation cohort on cycle 1, day 15; cycle 2, days 1 and 15; and cycles 3 and 4, day 1. PK analysis details are listed in the Data Supplement.

Overall response rate (ORR), complete response (CR), partial response (PR), stable disease (SD), and progressive disease were evaluated by the treating physician using the revised RECIST guideline (version 1.1).27

Biomarker Analysis
Patients were selected based on Clinical Laboratory Improvement Amendments–certified laboratory testing for MET alterations by RT-PCR, IHC, FISH, or next-generation sequencing (NGS; MET exon 14 alteration or amplification). Additional testing was done by Foundation Medicine (Boston, MA) for NGS and Clarient (Aliso Viejo, CA) for IHC and FISH. MET IHC positivity was defined as a score of 2+ or 3+, indicating ≥ 50% of tumor cells with moderate- or strong-intensity staining, respectively. Analysis of HGF levels was conducted in duplicate by enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN; Cat DHG00) as per the manufacturer’s instructions.

Statistical Methods
All patients who had at least one dose of study therapy were included in the analyses. Data were summarized by study phase and dose group. DLT meetings were conducted to determine whether to proceed to the next dose level. For continuous variables, summary statistics included mean,
RESULTS

From August 2013 to August 2017, 35 patients with MET-positive, stage IV NSCLC were enrolled at UCD and UCSF. Eighteen patients were enrolled into six dose-escalation cohorts. Twelve and five patients were enrolled in cohorts A and B, respectively (Fig 1).

Patient Demographics and Disease Characteristics

Patient demographics and disease characteristics are listed in Table 1. The median age was 65 years, and most patients were female (60%), white (80%), and had an ECOG PS of 0 (65.7%).

In the dose-escalation cohorts, nine (50%) patients had EGFR-positive tumors and two had T790M alterations (Fig 2). EGFR alterations are listed in Figure 2.

Prior treatments are outlined in Table 1. In the dose-escalation cohort and cohort A, 67% (patients 1 and 3-13) and 92% (all except patient 29) had prior treatment with at least one EGFR TKI. Three patients (patients 26, 33, and 28) had prior immunotherapy. Across the cohorts, two patients (patients 7 and 8) received prior treatment with a MET-targeted agent (cabozantinib).

For all patients with EGFR activating mutations (n = 21), except patients 7, 9, 23, and 33, the immediate prior treatment regimen was EGFR TKI monotherapy or in combination with other treatments (pembrolizumab, n = 2; MK2206 [AKT inhibitor], n = 1; cabozantinib, n = 2).

In cohort A, six (50%) patients had tumors with 3+ MET by IHC and five (42%) had 2+ IHC expression (Fig 2). Patient 22’s tumor showed MET amplification by NGS (> 10 copies); however, by FISH the tumor had equivocal amplification, with MET/CEN7 ratio of 1.1. In patient 21, FISH demonstrated a MET/CEN7 ratio of 3.4, consistent with the amplification observed by NGS. MET amplification was not observed in tumor samples from the other nine patients in cohort A. In cohort B, three of the five patients had MET exon 14 mutations (patients 24, 25, and 32), and one patient (patient 20), had MET amplification by NGS; however, this was equivocal by FISH (MET/CEN7 = 1.2;...
Fig 2). A waterfall plot of best response for all evaluable patients is shown in Figure 3.

**AEs**

The AEs that were possibly, probably, or definitely attributed to the study drugs are shown in Table 2 for all dose levels. Thirty-two patients developed an AE (91.4%) of any grade, with 12 (34.2%) patients developing a grade 3 or higher AE. The most common AEs of any grade were acneiform rash (62.9%), fatigue (51%), nausea (45.7%), diarrhea, lower extremity edema, vomiting, and hypoalbuminemia (37% each). The most common grade 3 or higher AEs were anorexia and increased lipase (5.7% each). In patients who received the recommended phase II dose (RP2D), the most common AEs were acneiform rash (65%), fatigue and nausea (both 60%), vomiting (55%), and hypoalbuminemia and edema (both 50%); additional AEs are detailed in Appendix Table A1. There were no grade 5 toxicities related to the drug combination.

**DLT and MTD**

In dose level 5, one patient developed grade 3 neutropenia possibly related to treatment. Dose level 6 served as the expansion of dose level 5, given that 600-mg capsules were previously shown to be pharmacokinetically equivalent to 400-mg tablets. No patients in dose level 6 experienced a DLT. The RP2D was capmatinib 400-mg tablets twice a day with erlotinib 150 mg daily.

**Dose Modification**

During study procedures, 15 patients received dose modifications. Six patients received dose modifications of capmatinib due to nausea (2), ALT abnormalities (1), edema (1), low neutrophil count (1), and elevated amylase (1). Five patients received dose modifications of erlotinib due to paronychia (2), acneiform rash (1), creatinine increase (1), and diarrhea (1). Four patients received dose modifications of both drugs for lipase elevation (1), creatinine increase (1), lymphopenia (1), and lung inflammation/pneumonitis (1).

**PK**

The PK properties of erlotinib and capmatinib were examined during dose escalation on cycle 1, day 15 at multiple time points after drug administration. The PK profiles of erlotinib and capmatinib are presented in Appendix Figure A1, and estimated PK parameters are shown in Appendix Table A2. Capmatinib exposure appears proportional with an increase of dose from 100 to 200 mg.
twice a day dose range, but were not dose proportional from 100 to 600 mg (Appendix Fig A1A and Appendix Table A2) in the presence of 150 mg of erlotinib. Coadministration of erlotinib slightly reduced systemic exposure to capmatinib; however, it was not statistically significant. The same 400-mg dose of capmatinib in the tablet formulation demonstrates a higher drug exposure with greater variation (Appendix Table A2) compared with the capsule formulation, although it was not statistically significant. In addition, erlotinib showed a dose-dependent change of systemic drug exposure (150 mg v 100 mg; Appendix Fig A1B and Appendix Table A2); coadministration with capmatinib did not have significant impact on erlotinib PK (Appendix Table A2). Overall, the range of erlotinib exposures during dose escalation was similar to previously published results.28

**Efficacy**

Across all evaluable patients, the ORR was 31% (8/26; Fig 3). Six of the eight patients with a PR or CR had MET amplification by FISH, NGS, or both. Two of the six patients with MET amplification also had MET exon 14 mutations. Of the eight patients with PR or CR, the four EGFR-positive patients had MET amplification by FISH, NGS, or both. The remaining one patient (patient 17) with MET exon 14 mutation and equivocal amplification had SD. Across all patients, the median PFS was 3 months. Among patients with PR or CR, the responses were prolonged, apart from patient 24, who discontinued study after 3 months because of pneumonia/pneumonitis; investigators could not rule out possible drug-related pneumonitis, and thus the patient was discontinued from study. Two responders were treatment naïve (20 and 24); the remainder had at least one prior regimen (Table 1).

**Dose-Escalation Cohort**

Fifteen of the 18 patients in the dose-escalation cohort were evaluable. For two patients (patients 5 and 14), the only RECIST measurable lesions became unmeasurable during treatment. The third patient (patient 15) developed symptomatic brain metastases after one dose of study drug and discontinued study. Patient 16 (EGFR WT, MET IHC 3+) on dose level 6 had a CR. Ten patients demonstrated SD. Of the evaluable patients in the dose-escalation cohort, the ORR was 7% (n = 1/15), and the disease control rate (DCR) was 73% (n = 11/15; Table 3).

**Expansion Cohorts**

In expansion cohort A, eight of 12 patients with EGFR activating mutations with acquired resistance to an EGFR TKI were response evaluable. Two patients (patients 21 and 23) withdrew from the study by individual choice, one patient (patient 33) developed new brain metastasis and withdrew, and one patient (patient 30) had a prolonged hospitalization for a cerebrovascular event deemed unrelated to study drugs. Despite the small numbers of patients, both the ORR and DCR in this group were 50% (four patients; Table 4). Patients were on treatment of a median of 2 cycles (range, 1-33 cycles). Patient 22, who had a CR, harbored an EGFR L858R mutation and MET amplification and an IHC 3+ score. Patients 26 and 27 both had PRs with EGFR alterations, exon 19 deletion and L858R, respectively, and IHC 3+ but did not demonstrate MET amplification.
Five EGFR-WT patients were enrolled in cohort B; one patient (patient 25) was not evaluable because of death during cycle 1 deemed unrelated to the study drugs. The ORR and DCR were both 75% (3/4 patients), and patients were on treatment of a median of three cycles (range, 1-45 cycles; Table 4). All three responding patients had a MET IHC score of 3+, two had MET exon 14 mutations (patients 24 and 32), and one had MET amplification (patient 20; Figs 2 and 3). Notably, patient 32, with a MET exon 14 mutation, is still on treatment with response.

**DISCUSSION**

MET alterations are well-established mediators of EGFR TKI resistance. Given that MET and EGFR have overlapping and complementary activation of growth and proliferation pathways, the clinical evaluation of the combination of MET and EGFR TKIs as a potential strategy to improve EGFR TKI activity and prevent/overcome MET-driven EGFR-TKI resistance in EGFR-mutant NSCLC is rational. In this study, we demonstrated that standard-dose erlotinib can be safely combined with capmatinib.

**TABLE 4.** Efficacy Data Across Dose-Expansion Cohorts

| Dose Level | 1 | 2 | 3 | 4 | 5 | 6 |
|------------|---|---|---|---|---|---|
| INC280, mg twice daily | 100 | 100 | 200 | 400 | 600 | 400 |
| Erlotinib, mg once daily | 150 | 150 | 150 | 150 | 150 | 150 |
| Evaluable patients | 8 | 2 | 3 | 3 | 1 | 2 |
| Median cycles (range) | 2 (1-33) | 3 (1-45) | 2 (1-45) | 2 (1-45) | 4 (1-10) | 4 (4-29) |
| Complete response | 0 | 1 | 0 | 0 | 0 | 1 |
| Partial response | 0 | 0 | 0 | 0 | 0 | 0 |
| Stable disease | 2 | 2 | 1 | 2 | 1 | 2 |
| Progressive disease | 0 | 0 | 2 | 1 | 0 | 0 |
| Overall response rate | 0 | 0 | 0 | 0 | 0 | 1 (33%) |
| Disease control rate | 2 (67%) | 2 (67%) | 1 (33%) | 2 (67%) | 1 (33%) | 3 (100%) |

Abbreviation: INC280, capmatinib.

At the recommended phase II dosing, responses were seen in patients with MET amplification by NGS and/or 3+ IHC expression and those with MET exon 14 mutations, but not in patients with 2+ IHC expression. A study in Chinese patients with gefitinib plus capmatinib also reported that 2+ IHC expression was not predictive of response unless it was accompanied by a gene copy number of ≥ 5. The MET/CEN7 ratios were not fully reported in this study, but a ratio > 2.2 is considered positive. In addition, recently presented data demonstrated an ORR of 29% in previously treated and 40% in first-line patients with MET amplification treated with capmatinib. These collective findings demonstrate that MET amplification is a predictive biomarker of response to MET-TKIs.

Since initiation of the current study, MET exon 14 mutations were demonstrated to be predictive of response to crizotinib as well as capmatinib. Given this, cohort B, which was originally designed to determine whether there was a signal for response in EGFR mutant--negative, MET-positive patients, evolved to focus on cases with MET exon 14 mutation. The therapeutic contribution of erlotinib in these patients, if any, cannot be disentangled and should be evaluated in a larger study. Overall, our study is consistent with several reports showing efficacy in EGFR WT patients with MET exon 14 mutation or MET amplification.

Hepatocyte growth factor is the principal ligand for the MET receptor. Serial blood HGF levels were measured to evaluate baseline levels and treatment-related changes in patients over time; however, no overt correlations with baseline HGF levels and treatment outcomes were observed (data not shown).

The patient population with the greatest potential to benefit from the combination treatment was cohort A, which enrolled EGFR-positive patients who had experienced progression on EGFR TKIs. Four of nine evaluable patients showed durable benefit from combination capmatinib and erlotinib. These results are consistent with those from the...
TATTON trial (ClinicalTrials.gov identifier: NCT02143466) of osimertinib plus savolitinib (a selective and potent MET inhibitor) in patients with EGFR-mutated, T790M-negative tumors who have failed an EGFR TKI and with evidence of MET dysregulation.35,36 Our slightly lower ORR can be attributed to the inclusion of four patients with T790M and/or C797S resistance mutations, all of whom did poorly. Limitations to this study include the study design, which was executed before the more nuanced recognition of the best methods for detecting predictive MET abnormalities and before the oncogenic activity of MET exon 14 mutations was fully clarified.37,38 Second, we cannot delineate whether there is any additional benefit from the addition of erlotinib to single-agent capmatinib in patients with EGFR WT NSCLC with MET amplification and exon 14 mutations. Finally, we acknowledge that differences in testing modalities and “positivity” determinations remain a challenge for MET amplification.14

In conclusion, we have demonstrated that full doses of capmatinib and erlotinib can be safely co-administered. More work is needed to determine whether combination therapies are effective in TKI-naïve patients. As MET amplification is a major mechanism of osimertinib resistance, the evaluation of capmatinib with osimertinib may provide more durable response to treatment as frontline therapy than monotherapy. Additional evaluation of an EGFR-TKI plus a MET-TKI to overcome this common resistance mechanism is warranted.

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**FIG A1.** Pharmacokinetic profiles of patients in dose escalation. (A) Capmatinib (C) concentration as a function of time and erlotinib (E) dosing. (B) E concentration as a function of time and dose of C. BID, twice a day; D, daily.
| Adverse Event                               | Dose Level 1 |   |   | Dose Level 2 |   |   |   | Dose Level 3 |   |   |   | Dose Level 4 |   |   |   | Dose Level 5 |   |   |   | Dose Level 6 |   |   |   | Expansion |   |   | SAE | Total |
|--------------------------------------------|--------------|---|---|-------------|---|---|---|-------------|---|---|---|-------------|---|---|---|-------------|---|---|---|-----------|---|---|---|----------|---|---|---|---------|---|---|---|
| Rash (acneiform/ maculopapular)            | 2            | 0 | 2 | 0           |   |   |   | 2           | 0 | 1 | 0 | 2           | 0 | 1 | 0 | 12         | 0 | 0 | 12 | 22       |     |     |     |         |     |     |     |         |     |     |     |
| Fatigue                                    | 1            | 0 | 1 | 0           |   |   |   | 1           | 0 | 2 | 0 | 1           | 0 | 2 | 0 | 10         | 0 | 0 | 10 | 18       |     |     |     |         |     |     |     |         |     |     |     |
| Nausea                                     | 0            | 0 | 2 | 0           |   |   |   | 1           | 0 | 0 | 0 | 1           | 0 | 2 | 0 | 9          | 1 | 0 | 9  | 16       |     |     |     |         |     |     |     |         |     |     |     |
| Diarrhea                                   | 1            | 0 | 2 | 0           |   |   |   | 2           | 0 | 0 | 0 | 2           | 0 | 0 | 0 | 4          | 1 | * | 4  | 14       |     |     |     |         |     |     |     |         |     |     |     |
| Edema limbs                                | 0            | 0 | 1 | 0           |   |   |   | 1           | 0 | 0 | 0 | 1           | 0 | 2 | 0 | 6          | 2 |   | 6  | 13       |     |     |     |         |     |     |     |         |     |     |     |
| Hypoalbuminemia                            | 0            | 0 | 1 | 0           |   |   |   | 0           | 0 | 1 | 0 | 1           | 0 | 1 | 0 | 9          | 0 | 0 | 9  | 13       |     |     |     |         |     |     |     |         |     |     |     |
| Vomiting                                   | 0            | 0 | 0 | 1           | 0 | 1 | 0 | 1           | 0 | 1 | 0 | 1           | 0 | 1 | 0 | 10         | 0 | 0 | 10 | 13       |     |     |     |         |     |     |     |         |     |     |     |
| Lymphocyte count decreased                 | 0            | 0 | 0 | 0           |   |   |   | 1           | 0 | 0 | 0 | 1           | 0 | 1 | 0 | 5          | 2 |   | 5  | 12       |     |     |     |         |     |     |     |         |     |     |     |
| Anemia                                     | 0            | 0 | 0 | 0           |   |   |   | 0           | 0 | 1 | 0 | 1           | 0 | 2 | 0 | 7          | 0 | 0 | 7  | 13       |     |     |     |         |     |     |     |         |     |     |     |
| Paronychia                                 | 0            | 0 | 1 | 0           |   |   |   | 1           | 0 | 1 | 0 | 2           | 0 | 0 | 0 | 5          | 0 | 0 | 5  | 10       |     |     |     |         |     |     |     |         |     |     |     |
| Anorexia                                   | 0            | 1 | 2 | 0           |   |   |   | 1           | 0 | 0 | 0 | 0           | 0 | 1 | 0 | 2          | 0 | 2 | 2  | 9        |     |     |     |         |     |     |     |         |     |     |     |
| Alanine aminotransferase increased         | 1            | 0 | 1 | 0           |   |   |   | 1           | 0 | 0 | 0 | 0           | 0 | 1 | 0 | 3          | 1 | * | 3  | 8        |     |     |     |         |     |     |     |         |     |     |     |
| Alkaline phosphatase increased             | 2            | 0 | 2 | 0           |   |   |   | 0           | 0 | 0 | 0 | 0           | 0 | 1 | 0 | 2          | 0 |   | 2  | 7        |     |     |     |         |     |     |     |         |     |     |     |
| AST increased                              | 1            | 0 | 1 | 0           |   |   |   | 0           | 0 | 0 | 0 | 1           | 0 | 0 | 0 | 3          | 1 |   | 3  | 7        |     |     |     |         |     |     |     |         |     |     |     |
| Lipase increased                           | 0            | 0 | 1 | 1           |   |   |   | 0           | 0 | 0 | 0 | 0           | 0 | 0 | 0 | 4          | 1 |   | 4  | 7        |     |     |     |         |     |     |     |         |     |     |     |
| Dry skin                                   | 0            | 0 | 0 | 0           |   |   |   | 0           | 0 | 1 | 0 | 1           | 0 | 1 | 0 | 3          | 0 |   | 3  | 6        |     |     |     |         |     |     |     |         |     |     |     |
| Serum amylase increased                    | 0            | 0 | 2 | 0           |   |   |   | 0           | 0 | 1 | 0 | 0           | 0 | 0 | 0 | 3          | 0 |   | 3  | 6        |     |     |     |         |     |     |     |         |     |     |     |
| WBC decreased                              | 0            | 0 | 0 | 0           |   |   |   | 0           | 0 | 0 | 0 | 1           | 0 | 2 | 0 | 3          | 0 |   | 3  | 6        |     |     |     |         |     |     |     |         |     |     |     |
| INR increased                              | 0            | 0 | 0 | 0           |   |   |   | 1           | 0 | 0 | 0 | 0           | 0 | 0 | 0 | 4          | 1 |   | 4  | 6        |     |     |     |         |     |     |     |         |     |     |     |
| Creatinine increased                       | 0            | 0 | 0 | 0           |   |   |   | 0           | 0 | 0 | 0 | 0           | 0 | 0 | 0 | 6          | 0 |   | 6  | 6        |     |     |     |         |     |     |     |         |     |     |     |
| Pruritus                                   | 0            | 0 | 0 | 0           |   |   |   | 0           | 0 | 0 | 0 | 0           | 2 | 0 | 1 | 0          | 2 |   | 2  | 5        |     |     |     |         |     |     |     |         |     |     |     |
| Blood bilirubin increased                  | 0            | 0 | 0 | 0           |   |   |   | 0           | 0 | 1 | 0 | 0           | 0 | 1 | 0 | 3          | 0 |   | 3  | 5        |     |     |     |         |     |     |     |         |     |     |     |
| Dizziness                                  | 0            | 0 | 0 | 0           |   |   |   | 0           | 0 | 0 | 0 | 1           | 0 | 1 | 0 | 3          | 0 |   | 3  | 5        |     |     |     |         |     |     |     |         |     |     |     |
| Dysgeusia                                  | 1            | 0 | 0 | 0           |   |   |   | 0           | 0 | 0 | 0 | 0           | 0 | 0 | 0 | 3          | 0 |   | 3  | 5        |     |     |     |         |     |     |     |         |     |     |     |
| Headache                                   | 0            | 0 | 0 | 0           |   |   |   | 0           | 0 | 0 | 0 | 0           | 0 | 1 | 0 | 4          | 0 |   | 4  | 5        |     |     |     |         |     |     |     |         |     |     |     |
| Generalized muscle weakness                | 1            | 0 | 0 | 0           |   |   |   | 0           | 0 | 1 | 0 | 0           | 0 | 1 | 0 | 1          | 0 |   | 1  | 4        |     |     |     |         |     |     |     |         |     |     |     |
| Nail changes                               | 1            | 0 | 1 | 0           |   |   |   | 0           | 0 | 0 | 0 | 1           | 0 | 0 | 0 | 1          | 0 |   | 1  | 4        |     |     |     |         |     |     |     |         |     |     |     |
| Abdominal pain                             | 0            | 0 | 0 | 0           |   |   |   | 0           | 0 | 0 | 0 | 0           | 0 | 1 | 0 | 3          | 0 |   | 3  | 4        |     |     |     |         |     |     |     |         |     |     |     |

(Continued on following page)
| Adverse Event                  | Dose Level 1 | Dose Level 2 | Dose Level 3 | Dose Level 4 | Dose Level 5 | Dose Level 6 | Expansion |
|-------------------------------|--------------|--------------|--------------|--------------|--------------|--------------|-----------|
| Gastroesophageal reflux disease | 0            | 0            | 1            | 0            | 0            | 0            | 0         |
| Oral mucositis                | 0            | 0            | 0            | 0            | 0            | 0            | 0         |
| Hyponatremia                  | 0            | 0            | 0            | 0            | 0            | 0            | 0         |
| Stroke                        | 0            | 0            | 0            | 0            | 0            | 0            | 0         |
| Proteinuria                   | 0            | 0            | 1            | 0            | 0            | 0            | 0         |
| Back pain                     | 0            | 0            | 0            | 0            | 0            | 0            | 0         |
| Peripheral sensory neuropathy | 0            | 0            | 0            | 0            | 0            | 0            | 0         |

Abbreviations: Gr, grade; INR, international normalized ratio; SAE, significant adverse event. (*) Indicates SAE occurred.
| Cohort                                      | C<sub>max</sub> (ng/mL) | C<sub>min</sub> (ng/mL) | C<sub>trough</sub> (ng/mL) | AUC<sub>ss</sub> (mg/L*h) | C<sub>average</sub> (ng/mL) | CL<sub>ss</sub> (L/h) |
|--------------------------------------------|------------------------|------------------------|---------------------------|---------------------------|----------------------------|----------------------|
| Erlotinib                                  |                        |                        |                           |                           |                            |                      |
| Cohort 1 (C 100 mg twice a day/E 100 mg once daily) | 1,797 ± 666            | 870 ± 251              | 1,244 ± 441               | 27.0 ± 6.7                | 1,124 ± 279               | 3.9 ± 0.9            |
| Cohort 2 (C 100 mg twice a day/E 150 mg once daily) | 2,137 ± 386            | 1,243 ± 91             | 2,071 ± 384               | 39.3 ± 5.4                | 1,638 ± 223               | 3.9 ± 0.5            |
| Cohort 3 (C 200 mg twice a day/E 150 mg once daily) | 2,087 ± 691            | 601 ± 406              | 1,077 ± 890               | 27.5 ± 9.3                | 1,144 ± 389               | 6.0 ± 2.5            |
| Cohort 4 (C 400 mg twice a day/E 150 mg once daily) | 1,613 ± 485            | 642 ± 114              | 1,333 ± 546               | 22.1 ± 2.9                | 923 ± 123                 | 6.8 ± 0.9            |
| Cohort 5 (C 600 mg twice a day/E 150 mg once daily) | 1,380 ± 198            | 872 ± 223              | 985 ± 194                 | 23.6 ± 3.3                | 983 ± 137                 | 6.4 ± 0.9            |
| Cohort 6 (C 400 mg twice a day tablets/E 150 mg once daily) | 2,097 ± 909            | 880 ± 358              | 1,402 ± 699               | 29.6 ± 9.5                | 1,233 ± 395               | 5.4 ± 1.6            |
| Capmatinib                                 |                        |                        |                           |                           |                            |                      |
| Cohort 1 (C 100 mg twice daily/E 100 mg once daily) | 977 ± 640              | 167 ± 111              | 298 ± 250                 | 7.4 ± 4.9                 | 309 ± 205                 | 18.1 ± 11.2          |
| Cohort 2 (C 100 mg twice a day/E 150 mg once daily) | 617 ± 320              | 102 ± 50               | 144 ± 99                  | 4.9 ± 1.6                 | 205 ± 67                  | 22.1 ± 8.2           |
| Cohort 3 (C 200 mg twice a day/E 150 mg once daily) | 1,827 ± 784            | 181 ± 164              | 248 ± 150                 | 11.7 ± 4.5                | 488 ± 188                 | 19.5 ± 9.6           |
| Cohort 4 (C 400 mg twice a day/E 150 mg once daily) | 5,930 ± 1,461          | 493 ± 249              | 549 ± 450                 | 35.9 ± 6.9                | 1,495 ± 287               | 11.4 ± 2.0           |
| Cohort 5 (C 600 mg twice a day/E 150 mg once daily) | 13,500 ± 848           | 2,516 ± 3,555          | 4,106 ± 2,334             | 162 ± 133                 | 6,735 ± 5,546             | 5.6 ± 4.6            |
| Cohort 6 (C 400 mg twice a day tablets/E 150 mg once daily) | 11,490 ± 7,370         | 1,390 ± 1,845          | 3,288 ± 4,688             | 122 ± 126                 | 5,064 ± 5,251             | 6.0 ± 3.9            |

Abbreviations: AUC<sub>ss</sub>, area under the curve, steady state; C, capmatinib; C<sub>average</sub>, average concentration; CL<sub>ss</sub>, apparent total body clearance of drug from plasma at steady state; C<sub>max</sub>, maximum concentration of drug; C<sub>min</sub>, minimum concentration of drug; C<sub>trough</sub>, trough plasma concentration; E, erlotinib; PK, pharmacokinetic.