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Dovitinib and erlotinib in patients with metastatic non-small cell lung cancer: A drug–drug interaction

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Abstract

Introduction—Erlotinib is a FDA approved small molecule inhibitor of epidermal growth factor receptor and dovitinib is a novel small molecule inhibitor of fibroblast growth factor and vascular endothelial growth factor receptor. This phase 1 trial was conducted to characterize the safety and determine the maximum tolerated dose of erlotinib plus dovitinib in patients with previously treated metastatic non-small cell lung cancer.

Methods—Escalating dose cohorts of daily erlotinib and dovitinib dosed 5 days on/2 days off, starting after a 2-week lead-in of erlotinib alone, were planned. A potential pharmacokinetic interaction was hypothesized as dovitinib induces CYP1A1/1A2. Only cohort 1 (150 mg erlotinib + 300 mg dovitinib) and cohort -1 (150 mg erlotinib + 200 mg dovitinib) enrolled. Plasma concentrations of erlotinib were measured pre-and post-dovitinib exposure.

Results—Two of three patients in cohort 1 had a DLT (grade 3 transaminitis and grade 3 syncope). Two of 6 patients in cohort -1 had a DLT (grade 3 pulmonary embolism and grade 3 fatigue); thus, the study was terminated. Erlotinib exposure (average C_{max} 2308 ± 698 ng/ml and AUC_{0–24} 41,030 ± 15,577 ng × h/ml) approximated previous reports in the six patients with pharmacokinetic analysis. However, erlotinib C_{max} and AUC_{0–24} decreased significantly by 93% ($p = 0.02$) and 97% ($p < 0.01$), respectively, during dovitinib co-administration.

Conclusions—This small study demonstrated considerable toxicity and a significant pharmacokinetic interaction with a marked decrease in erlotinib exposure in the presence of dovitinib, likely mediated through CYP1A1/1A2 induction. Given the toxicity and the pharmacokinetic interaction, further investigation with this drug combination will not be pursued.

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Conflict of interest

The authors declare that they have no conflict of interest.

Keywords

Dovitinib; Erlotinib; TKI 258; NSCLC; Epidermal growth factor receptor (EGFR)

1. Introduction

Erlotinib, afatinib, and gefitinib are epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) that are effective in treating non-small cell lung cancer (NSCLC) patients with known EGFR activating mutations, with response rates (RRs) of ~60–70% and a significant improvement in progression-free survival (PFS) when compared with platinum-based chemotherapy. Unfortunately, resistance develops in the majority of patients in less than 1 year. [1–3] In unselected patients, RRs are very low with EGFR TKIs, but PFS and overall survival (OS) benefits have been documented when compared to placebo in the refractory setting. [4] Exploration of strategies to improve the efficacy of these agents in patients without EGFR activating mutations, to delay development of resistance in those with EGFR activating mutations, and to overcome resistance once it develops is critical. One such approach is to combine EGFR TKIs with other targeted agents, in particular those targeting angiogenesis via the vascular endothelial growth factor (VEGF)/VEGF-receptor (VEGF-R) pathway. [5] Two separate phase III trials in an unselected NSCLC population demonstrated improvement in both PFS and RR with the combination of erlotinib and bevacizumab (monoclonal antibody against VEGF) compared to either agent alone, with some signal for improved activity in the EGFR mutant subgroups. [6,7] More recent literature strongly suggests an additive effect on PFS with the addition of bevacizumab to erlotinib in patients with EGFR mutant NSCLC (16.0 vs. 9.7 months, respectively, hazard ratio 0.54, $p = 0.0015$). [8]

Dovitinib, an oral multi-targeted receptor TKI, has a unique inhibition profile including activity against VEGFR, fibroblast growth factor receptor (FGFR), platelet derived growth factor receptor (PDGFR), and fms-related tyrosine kinase 3 (FLT-3) among other targets. This agent has demonstrated anti-tumor activity in patients with a variety of advanced solid tumors with an acceptable side effect profile, with the most common adverse events including fatigue and gastrointestinal toxicities (nausea, vomiting, anorexia, and diarrhea). [9] Compared to other VEGFR TKI agents such as sorafenib and sunitinib, dovitinib additionally targets FGFR, which contributes to growth, survival, and migration of NSCLC cells and may also be an important escape mechanism of anti-VEGFR therapy. [10] Unfortunately, despite this potential advantage, dovitinib did not provide benefit over sorafenib in the third-line setting for a different tumor type, renal cell carcinoma. [11] Furthermore, in those patients with intrinsic or acquired resistance to EGFR TKIs, FGFR may be an alternate signaling pathway contributing to NSCLC cell survival. [12–14] Indeed, the combined blockade of EGFR and FGFR was found to exert synergistic anti-proliferative effects in NSCLC preclinical models, warranting further study. [15] Thus, we conducted a phase I trial evaluating the combination of erlotinib and dovitinib for the treatment of patients with advanced NSCLC progressing after one or more prior therapies (Clinicaltrials.gov Identifier: NCT01515969). The primary objectives of the study were to characterize the safety and tolerability of the combination of erlotinib and dovitinib and to

establish the maximum tolerated dose (MTD). Secondary objectives included assessment of the initial efficacy of the combination, as well as to evaluate the potential impact of dovitinib on erlotinib pharmacokinetics (PK), especially given that dovitinib is known to induce CYP1A1/1A2, which is partially responsible for erlotinib metabolism.

2. Materials and methods

2.1. Patient selection

Patients with histologically confirmed metastatic NSCLC who had failed at least 1 prior therapy, including those previously treated with erlotinib, were considered eligible for the study. The presence of an EGFR mutation was not required. Additional eligibility criteria included: 1 measurable lesion by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria, age ≥ 18 years, Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 , life expectancy > 2 months, and adequate hematopoietic, hepatic, and renal function. Enrollment exclusions included patients who had received prior systemic anti-cancer therapy, radiation, or major surgery within pre-specified time-frames required for washout/recovery; history of other primary cancer within 3 years (except non-melanoma skin cancer and resected cervical carcinoma *in situ*); pregnant or breastfeeding females; active or chronic hepatitis B or C with impaired hepatic function [aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $> 2.5X$ upper limit of normal (ULN)]; active smoking (smoking decreases serum levels of erlotinib via induction of CYP1A1/1A2) [16]; history of pulmonary embolism (PE) in last 6 months or those receiving anticoagulation treatment with therapeutic doses of warfarin or enoxaparin; interstitial pneumonitis or fibrosis; and other severe or uncontrolled medical conditions within 6 months of enrollment (i.e. left ventricular ejection fraction $< 50\%$). The protocol was approved by our institutional review board and conducted in accordance with Good Clinical Practice guidelines. All patients provided written informed consent.

2.2. Study design and treatment plan

This was a single-site phase I standard 3 + 3 dose escalation trial of erlotinib and dovitinib in patients with EGFR wild-type or mutant metastatic NSCLC who could have previously received erlotinib. Four cohorts were planned with erlotinib dosed orally daily and dovitinib dosed orally 5 days on/2 days off, starting after a 2-week lead-in of erlotinib alone. Both erlotinib and dovitinib were taken without food, although it is now known that food does not alter the bioavailability of dovitinib. [17] The initial cohort included 3 patients (cohort 1): erlotinib 150 mg and dovitinib 300 mg. Blood samples for drug level measurements were collected on day 14 ± 4 (erlotinib alone; pre-dose, 2, 4, 6, 8, and 24 h) at erlotinib steady state (median half-life is 36.2 h). [18] Thereafter, dovitinib was added and blood samples for drug level measurements were collected on day 29 ± 4 (dovitinib + erlotinib; pre-dose, 2, 4, 6, 8, and 24 h). Patients continued on treatment until disease progression or unacceptable toxicity.

Dose escalation proceeded by standard 3 + 3 design. Dose limiting toxicity (DLT) was defined as $\geq$ grade 3 toxicity by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0 occurring during the first 3 weeks of

treatment with both drugs (after erlotinib lead-in time) with the exception of nausea, vomiting, diarrhea, or skin rash that was not optimally treated. If no DLTs occurred or 1 DLT occurred with appropriate cohort expansion from 3 to 6 patients after 3 weeks on both drugs (i.e. 5 weeks from the start of the erlotinib lead-in), dose escalation to cohort 2 would occur (erlotinib 300 mg and dovitinib 300 mg). The cohorts were built with the assumption that there may be a 20–50% reduction in the steady state concentration of erlotinib based upon CYP1A1/1A2 induction by dovitinib. [19] Therefore, cohort 2 was planned with a dose escalation of erlotinib to 300 mg based upon the results from a prior PK study with erlotinib and another CYP1A1/1A2 inducer, cigarette smoking. [16,20] Analysis of erlotinib PK from cohorts 1 and 2 was required prior to proceeding to the next cohort to ensure erlotinib levels were within therapeutic range. There was also a dose level -1 should cohort 1 not be tolerated. Only two cohorts enrolled due to DLTs [cohort 1 and (-1)] and cohort -1 was determined to surpass the MTD.

During the study, patients were monitored for safety on clinic visits day 1, 15, and 29 of cycle 1 and then once every cycle. Laboratory testing (blood chemistry, hematology) was performed weekly for the first cycle and then once per cycle. Concomitant medications were recorded throughout the study and pill count was employed to evaluate for compliance. Echocardiogram, cardiac enzymes (i.e. troponin), and an electrocardiogram (EKG) were performed at baseline. In addition, EKGs were performed on days 15 and 29 of cycle 1, and at the off-study evaluation. Tumor assessments were conducted at baseline and repeated every 8 weeks until disease progression using computed tomography imaging. Disease status was assessed by the investigator according to RECIST v1.1 criteria.

2.3. Pharmacokinetic analysis

PK parameters for erlotinib, erlotinib primary metabolite OSI-420, and dovitinib were estimated from plasma concentration data via standard noncompartmental analysis using Phoenix^{TM} WinNonlin® (version 6.3; Certara, St. Louis, MO). The maximum concentration (C_{max}) and corresponding time to maximum concentration (T_{max}) were obtained directly from the observed data. The terminal rate constant (λ_z) was determined by linear regression analysis of the terminal portion of the log plasma concentration–time curve, and the terminal half-life ($t_{1/2}$) was calculated as $\ln 2/\lambda_z$. Area under the curve from time 0 to 24 (AUC_{0-24}) was found using the linear/logarithmic trapezoidal method.

All PK parameters calculated were based on an erlotinib 150 mg dose and dovitinib 200 mg dose to allow for PK (i.e. C_{max} and AUC_{0-24}) summary statistics. One patient had a dose reduction in erlotinib from 150 mg to 100 mg during the erlotinib lead-in period, and one patient in cohort 1 received a 300 mg dose of dovitinib. These two patients' PK parameters were calculated as if they had received erlotinib 150 mg dose and dovitinib 200 mg dose, respectively. One patient was excluded from the OSI-420 analysis since all concentrations were below the lower limit of quantification (LLOQ) at day 29 ± 4 . PK parameters for erlotinib and OSI-420 were compared in patients pre- vs. post- dovitinib using the paired-t test ($\alpha < 0.05$, 2-sided) on log transformed data (STATA Version 13, Stat-aCorp, College Station, TX). In addition, the geometric mean ratio of post-dovitinib treatment values

relative to pre-dovitinib values (i.e. erlotinib alone) and their 95% confidence intervals were calculated.

2.4. Analytic methods

The concentrations of erlotinib and OSI-420 were measured using a high-pressure liquid chromatography–tandem mass spectrometry (HPLC-MS/MS) method at Quintiles (Durham, North Carolina, USA). For erlotinib, the range of the assay was 1–3000 ng/ml and for OSI-420, the range was 1–1000 ng/ml. Dovitinib was quantified in plasma using sorafenib as the internal standard, liquid-liquid extraction, and HPLC-MS/MS (ABSciex4000, Applied Biosystems; Indiana University, Indianapolis, IN), and the range of the assay was from 1–10,000 ng/ml.

3. Results

3.1. Patient characteristics

A total of 9 patients were enrolled (3 in cohort 1 and 6 in cohort -1) and were on study from July 24, 2012 until March 29, 2013. The majority of patients were women ($n = 6$), never smokers ($n = 6$), had an *EGFR* mutation (2 exon 19 deletion, 2 exon 21 L858R, and 2 exon 20 insertions), and had received prior erlotinib ($n = 6$, range 3.9 months-22 months; Table 1).

3.2. Dose limiting toxicities and safety profile

The study was suspended due to an excess of DLTs and the MTD was surpassed at the lowest dose cohort (cohort -1 erlotinib 150 mg and dovitinib 200 mg). Of the 3 patients in cohort 1, two had a DLT (grade 3 transaminitis and grade 3 syncope). Of the 6 patients in cohort -1, two had a DLT (grade 3 PE and grade 3 fatigue). An additional patient in cohort -1 had a grade 3 PE outside of the DLT time period after 6 weeks of treatment on both dovitinib and erlotinib. Overall, four patients discontinued due to adverse events (1 syncope, 1 fatigue, 2 PE). The patient in cohort 1 with a DLT due to grade 3 transaminitis was able to continue on study after rapid improvement to grade 2 and subsequent resolution after a dose hold for 3 days. One patient required a dose reduction of erlotinib to 100 mg prior to the initiation of dovitinib for grade 3 rash. There was no QT prolongation seen in this study. The most common toxicities included rash, diarrhea, dysphagia, and PE (Table 2).

3.3. Efficacy

Of the 9 patients, 2 patients stopped the study early due to toxicity prior to their next follow-up scan 34 days and 19 days later, respectively, but continued erlotinib monotherapy and are included. Five patients had a best response of stable disease and one patient had an unconfirmed partial response (Table 1). The average duration on study treatment for these 6 patients was 3.4 months (1–8 months). Three patients with stable disease came off study for a DLT and the patient with the unconfirmed partial response came off study for a PE outside of the DLT window. One patient, despite having a non-sensitizing *EGFR* mutation (exon 20 insertion), had a 21% decrease in the target lesions, and was on erlotinib alone at the time of repeat evaluation. The patient with stable disease for the longest period (8 months) had a *KRAS* G12A mutation. The patient with an unconfirmed partial response was suspected to

have an EGFR mutation because she had started on monotherapy with erlotinib before testing was routine and had a clear response for 14.2 months, although EGFR testing was never confirmed and the subtype therefore remains unknown.

3.4. Pharmacokinetics

Six patients had erlotinib PK sampling performed both pre-and post-dovitinib (1 from cohort 1 and 5 from cohort -1), but only 5 were evaluable for the OSI-420 metabolite. The mean concentration-time profiles of erlotinib and OSI-420 pre- and post-dovitinib are shown in Fig. 1. After starting dovitinib, all patients had a large decrease in erlotinib and OSI-420 exposure as measured by the C_{max} and AUC_{0-24h} (Fig. 2 and Table 3). During dovitinib co-administration, erlotinib C_{max} decreased by 93% ($p = 0.02$) and AUC_{0-24} decreased by 97% ($p < 0.01$). There was a similar significant decrease in OSI-420. When accounting for the large inter-patient variability, the PKs of erlotinib and OSI-420 before starting dovitinib were similar to historical controls. [18,21]

The mean PK parameters for dovitinib normalized to 200 mg were: C_{max} 219 ± 112 ng/ml, T_{max} 6.0 h (range 0–8), AUC_{0-24} 3865 ± 2185 ng/ml $\times$ h, and terminal $t_{1/2}$ 32 ± 19 h.

4. Discussion

Dovitinib plus erlotinib in previously treated NSCLC patients in this small study was poorly tolerated with an excess of DLTs. The most common toxicities regardless of grade reported in previous studies with dovitinib included diarrhea (68%), nausea (66.7%), vomiting (60.6%), fatigue (40.5%), and decreased appetite (37.0%). [9,22–24] These most common side effects were also seen in our study. However, the severity of toxicities in this small subset, particularly the two PE events, was more than predicted. Thromboembolic events ($n = 2$) have now been reported in another phase I study of dovitinib in combination with cisplatin and gemcitabine in patients with malignancies other than lung cancer. [25] Despite the toxicity, there were 2 patients in the study who had a significant decrease in target lesions after receiving the combination of dovitinib/erlotinib. One patient had a non-sensitizing EGFR mutation while the other had a suspected EGFR mutation with an unusually long survival of greater than 6 years from the time of diagnosis. As seen within our small study, it is possible that dual inhibition of EGFR and FGFR may benefit a particular subset of patients harboring an EGFR mutation, although given the significant toxicities seen with the combination of dovitinib/erlotinib, this may not be possible to explore further. In our study, there was also a significant drug–drug interaction, with a large reduction in erlotinib exposure seen with dovitinib co-administration. This study emphasizes the importance of performing phase I studies when combining small molecule TKIs, not only given the potential for significant PK interactions but also for unexpected toxicities.

In order to better understand the PK interaction observed in the current study, we review the metabolism of dovitinib and erlotinib below. Dovitinib *in vitro* is metabolized by FMO3 (65–83%), CYP3A4 (17–35%), and inducible enzymes CYP1A1/1A2. [19] Dovitinib is also a strong inducer of CYP1A2 as demonstrated by a caffeine study (CYP1A2 substrate) where it reduced the AUC of caffeine by 96%. [19] Erlotinib is metabolized by CYP3A4/3A5 and CYP1A1/1A2. [26] It is well known that strong CYP3A4 inducers decrease erlotinib

exposure and should be avoided while on therapy. For example, in a study with rifampin, there was a 29% decrease in $C_{\max}$ and a 66% decrease in AUC. [27] In scenarios where concomitant strong CYP3A4 inducers cannot be avoided, as with antiepileptic therapy in gliomas, it is suggested that the dose of erlotinib be increased to 450 mg. [28]

In lung cancer, the best studied effect of CYP1A1/1A2 induction on erlotinib exposure is secondary to cigarette smoking. In a healthy volunteer study evaluating the effects of smoking on erlotinib PK, the $C_{\max}$ after a 150 mg dose decreased by 35% in smokers (smokers: 689 ng/ml versus nonsmokers: 1056 ng/ml) and the AUC decreased by 64% (smokers: 6718 ng $\times$ h/mL versus non-smokers: 18,726 ng $\times$ h/mL). [16] Similarly, in NSCLC patients who currently smoke, the steady-state trough concentration was 2-fold lower compared to non-smokers. [29] Increasing the erlotinib dose in smokers from 150 mg to 300 mg results in drug levels similar to the standard 150 mg dose in nonsmokers. [20] Accordingly, dose escalation up to 300 mg is recommended for patients who currently smoke. [20]

In the current study, the decrease in erlotinib exposure after the start of dovitinib was larger ($C_{\max}$ and AUC_{0-24} were decreased by 93% and 97%, respectively) than that previously described for erlotinib in the presence of CYP1A1/1A2 (i.e. smoking) and CYP3A4 (i.e. rifampin) inducers. However, the size of the PK interaction observed is similar in magnitude to the reduction in caffeine exposure during dovitinib treatment as previously mentioned. [19] CYP1A1/1A2 induction by dovitinib is presumably the major mechanism behind the reduced erlotinib exposure seen in the current study. It is hypothesized that with strong induction, CYP1A1/1A2 becomes the major pathway for erlotinib metabolism. In addition, erlotinib metabolite exposure decreased during dovitinib treatment, which was also seen with CYP1A1/1A2 induction via smoking. [16] In reviewing the concomitant medications of each patient, there was no other obvious mechanism for the uniform decrease in erlotinib that was seen in all patients. Specifically, proton pump inhibitors were prohibited during the trial, and therefore the impact of pH-dependent solubility and reduced drug exposure was controlled. [29]

The large variation in dovitinib PK in the current study was most likely secondary to the timing of PK sampling during the 5 days on/2 days off schedule; however, this large inter-patient variability has been previously documented with dovitinib. [22] Overall, the dovitinib exposure was similar to prior reports when taking into account the timing of PK sampling. [19] Because of the small sample size, we are unable to correlate dovitinib PK with toxicity.

In conclusion, our small study demonstrates a significant PK interaction with decrease in the exposure of erlotinib and its metabolite in the presence of dovitinib, most likely via CYP1A1/A2 induction. This reduction in exposure is larger than that reported in prior combination studies with other CYP1A1/1A2 or CYP3A4 inducers. [20,27,28] Given the observed toxicity of the combination drug regimen even with highly reduced erlotinib exposure, further investigation with this drug combination will not be pursued. This study highlights the importance of performing rigorous phase I studies to evaluate toxicity and PK

interactions of novel drug combinations as neither the level of adverse events nor the degree of PK interaction was expected in our study.

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Fig 1. Erlotinib (a) and Metabolite OSI-420 (b) Concentration Over Time. Concentrations are normalized to a 150 mg dose. Six participants had evaluable concentrations for erlotinib and five for OSI-420. Values represent mean and error bars standard deviation.

Fig 2. The effect of co-administration of dovitinib on the AUC₀₋₂₄ of (a) Erlotinib and (b) Metabolite OSI-420 by participant. Values are normalized to a 150 mg dose.

Table 1

Demographics and best response.

Pt ^a	Sex	Age (yrs)	Ethnicity	Mutation status	Histology	Prior E (mo)	Smoking history	Best response (RECIST v 1.1) ^b	Duration on Study (mo)	Reason for study discontinuation	PK data available
1	M	62	Asian	KRAS G12A	Adenoca	5.9	Former (6 pack-years)	SD (0%)	8	PD ^e	Yes
2	F	67	White	EGFR exon 21 L858R	Adenoca	4.3	Never	SD ^c (0%)	1.1	DLT grade 3 syncope	No
3	M	40	Hispanic	EGFR exon 20 ins	Adenoca	0	Never	PD (3% ↓)	0.8	PD	No
4	F	76	White	EGFR exon 19 del	Adenoca	22	Light (0.03 pack-years)	SD ^d (1% ↑)	1	DLT grade 3 PE	Yes
5	M	53	White	None	Adeno-squam	0	Former (20 pack-years)	SD (13% ↑)	7.1	PD	Yes
6	F	50	Asian	EGFR (suspected, not confirmed)	Adenoca	14.2	Never	PR (40% ↓)	2	AE ^e	Yes
7	F	75	White	EGFR exon 19 del	Adenoca	3.9	Never	PD (3% ↑)	1.9	PD	Yes
8	F	50	Hispanic	EGFR exon 21 L858R and T790 M; ALK translocation	Adenoca	13.5	Never	PD (3% ↓)	2	PD	Yes
9	F	47	Asian	EGFR exon 20 ins	Adenoca	0	Never	SD ^c (21% ↓)	1.4	DLT grade 3 fatigue	No

Abbreviation: M = male; F = female; EGFR = epidermal growth factor receptor; ins = insertion; del = deletion; ALK = anaplastic lymphoma kinase rearrangement; adenoca = adenocarcinoma; adenosquam = adenosquamous; E = erlotinib; SD = stable disease; PD = progressive disease; PR = partial response; DLT = dose limiting toxicity; AE = adverse event; PE = pulmonary embolism; PK = pharmacokinetic

^aPatients 1–3 were in cohort 1 and patients 4–9 were in cohort -1.

^bPercentage change indicates maximum best response from baseline in target lesions. If best response is categorized as PD but there is not a 20% increase in the percentage of target lesions, this is explained by the development of new lesions.

^cPatient 2 and patient 9 stopped the study early due to toxicity prior to their next follow-up scan 34 days and 19 days later, respectively. Both patients, however, continued erlotinib monotherapy.

^dPatient 4 did not have all disease evaluable (i.e. liver metastases) on follow-up scan as only a CT chest was performed. However, this showed stable disease.

^ePatient 1 had a DLT of grade 3 transaminitis but it was transient and resolved quickly, and he was taken off study at PD. Patient 6 had a pulmonary embolism outside of the DLT window after 6 weeks of taking both dovitinib/erlotinib together.

Table 2

Adverse events regardless of relatedness.

Adverse events (AEs) Description	Grade 2 AEs% (n)	Grade 3 AEs% (n)
Rash	33 (3)	11 (1)
Diarrhea	33 (3)	0 (0)
Nausea/vomiting	11 (1)	0 (0)
Dysphagia	22 (2)	0 (0)
Anorexia	11 (1)	0 (0)
Pulmonary embolism	0 (0)	22 (2) ^a
Fatigue	11 (1)	11 (1) ^a
Syncope	0 (0)	11 (1) ^a
Headache	11 (1)	0 (0)
Pneumonia	11 (1)	0 (0)
Abdominal pain	11 (1)	0 (0)
Mucositis	0 (0)	11 (1)
AST/ALT elevation	0 (0)	11 (1) ^a
Hyponatremia	11 (1)	0 (0)

^aDose limiting toxicities include one each of pulmonary embolism, grade 3 AST/ALT elevation, grade 3 syncope, and grade 3 fatigue. The same patient with grade 3 fatigue also had grade 3 mucositis.

Table 3

Pharmacokinetic Parameters of Erlotinib and OSI-420 Metabolite.

Parameter	Erlotinib alone (E)(Day 14 ± 4)	Erlotinib + Dovitinib (E + D)(Day 29 ± 4)	Geometric mean ratio (D + E:E)	
			Mean	95% CI
Erlotinib–150 mg dose (<i>n</i> = 6) ^a				
<i>C</i> _{max} (ng/ml)	2308 ± 698	317 ± 303*	0.07	0.01–0.59
<i>T</i> _{max} (h)	3 (2–24)	3 (2–6)	–	–
<i>T</i> _{1/2} , terminal(h)	50 ± 53	5 ± 3*	0.10	0.02–0.42
AUC _{0–24h} (ng/ml × h)	41030 ± 15577	1858 ± 1790*	0.03	0.004–0.18
OSI-420 (<i>n</i> = 5) ^b				
<i>C</i> _{max} (ng/ml)	317 ± 166	56 ± 43*	0.17	0.07–0.40
AUC _{0–24h} (ng/ml × h)	5381 ± 2982	342 ± 252*	0.06	0.02–0.17

All values reported as mean ± standard deviation except *T*_{max} represented as median and range. All values with a (*) indicate a statistically significant change with the combination of erlotinib + dovitinib versus erlotinib alone at a 2-sided *p*-value < 0.05.

^aOne patient had a dose reduction in erlotinib from 150 mg to 100 mg and this patient's PK parameters were normalized to a 150 mg dose.

^bOne patient was excluded from OSI-420 analysis since all concentrations were below the lower limits of quantification at day 29 ± 4.