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ORIGINAL ARTICLE

A phase I dose-escalation and pharmacokinetic study of enzastaurin and erlotinib in patients with advanced solid tumors

Sukhmani K. Padda · Yelena Krupitskaya · Laveena Chhatwani · George A. Fisher · Alexander D. Colevas · Melanie San Pedro-Salcedo · Rodney Decker · Jane E. Latz · Heather A. Wakelee

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Abstract
Purpose Enzastaurin, an oral serine/threonine kinase inhibitor, targets the protein kinase C and AKT pathways with anti-tumor and anti-angiogenic effects. Erlotinib, an oral epidermal growth factor receptor (EGFR) inhibitor, has activity in solid tumors. Based on the promising combination of EGFR inhibitors and anti-angiogenic agents, this phase I trial was initiated.
Methods This single-institution, open-label, non-randomized trial used a standard 3 + 3 dose-escalation model in patients with advanced solid malignancies including non-small-cell lung cancer (NSCLC). Two dose levels of enzastaurin (with loading doses) were explored: 250 mg daily and 500 mg daily. Erlotinib was given at 150 mg daily.
Results Sixteen patients were enrolled in this study (median age, 64 years). Most patients were heavily pre-treated, female, and Caucasian and had NSCLC. The highest dose of enzastaurin, 500 mg daily, was tolerated with no unexpected adverse events and no alteration in the pharmacokinetics of either drug at this dose level. The mean clearance was 5.75 L/h for erlotinib and 53.8 L/h for enzastaurin. The most common possibly drug-related grade 3–4 adverse events included diarrhea (25.0%), neurologic symptoms (18.8%), and vomiting (18.8%). Activity was noted, with a partial response in one patient and prolonged disease stability for >12 cycles in three patients.
Conclusion The combination of enzastaurin 500 mg daily and erlotinib 150 mg daily is well tolerated and does not alter the pharmacokinetics of the individual drugs, with clinical activity seen. A phase II trial of this combination has been initiated in patients with advanced-stage NSCLC.

Keywords Clinical trial · Enzastaurin · Erlotinib · Pharmacokinetics

S. K. Padda · Y. Krupitskaya · L. Chhatwani · G. A. Fisher · A. D. Colevas · M. San Pedro-Salcedo · H. A. Wakelee (✉)
Department of Medicine, Division of Oncology, Stanford University, 875 Blake Wilbur Drive, Stanford, CA 94305-5826, USA
e-mail: Hwakelee@stanford.edu

S. K. Padda · Y. Krupitskaya · L. Chhatwani · G. A. Fisher · A. D. Colevas · M. San Pedro-Salcedo · H. A. Wakelee
Stanford Cancer Institute, Stanford, CA, USA

Present Address:
L. Chhatwani
Department of Medicine, Division of Pulmonary and Critical Care Medicine, Virginia Commonwealth University Medical Center, Richmond, VA, USA

R. Decker · J. E. Latz
Eli Lilly and Company, Indianapolis, IN, USA

Introduction

The treatment of solid tumors with targeted agents has shown promise, particularly with inhibitors of the epidermal growth factor receptor (EGFR) and angiogenic pathways. Enzastaurin, a novel targeted agent in the class of acyclic *N*-(azacycloalkyl) bisindolylmaleimides, is an oral serine/threonine kinase inhibitor that targets both the protein kinase C (PKC) and AKT pathways [1, 2]. PKC and AKT have been associated with tumorigenesis, treatment efficacy, and outcome in a variety of cancers, including non-small-cell lung cancer (NSCLC) [3–5]. In preclinical models, anti-tumor and anti-angiogenic activity of enzastaurin was demonstrated in various cancer cell lines and human cancer xenografts (including lung cancer) [2, 6]

and, in clinical studies, enzastaurin as a single agent was well tolerated up to 700 mg with early promising activity [7]. In a phase II study, single-agent enzastaurin as second- or third-line therapy in patients with metastatic NSCLC was well tolerated with some disease stabilization seen (11% with prolonged stabilization >6 months) [8].

Erlotinib, an EGFR-targeted tyrosine kinase inhibitor, has been shown to increase overall survival when combined with gemcitabine in pancreatic cancer [9] and as a second- or third-line single agent in NSCLC [10]. In NSCLC, erlotinib increased the response rate (8.9% vs. <1%, $P < 0.001$) and overall survival (6.7 months vs. 4.7 months; hazard ratio, 0.70; $P < 0.001$) compared with placebo in an unselected patient population [10].

Mechanisms of resistance to EGFR inhibitors include activation of the phosphoinositide 3-kinase (PI3 K)/AKT pathway [11, 12] and increased secretion of angiogenic factors including vascular endothelial growth factor (VEGF) [13]. Because enzastaurin suppresses VEGF-mediated angiogenesis through PKCß inhibition and inhibits the PI3 K/AKT pathway, it was hypothesized that the combination of erlotinib and enzastaurin would offer a mechanistic advantage. In preclinical models combining enzastaurin with gefitinib, an EGFR inhibitor similar in mechanism to erlotinib, synergism was found in a variety of both gefitinib-sensitive and gefitinib-resistant cancer cell lines [14].

In previous studies, when administered in combination with other agents, enzastaurin did not lead to an increased toxicity profile [15, 16]. Based on these promising data and the expected effects on common signaling pathways, a phase I/II study was initiated to evaluate the combination of enzastaurin and erlotinib; phase I results are presented here. As both drugs are metabolized through the liver cytochrome p450 CYP3A4 [7, 17], a dose-escalation trial was designed to ensure that there were no significant drug–drug interactions. The primary objective of the phase I portion of the trial was to determine the recommended phase II dose of the combination of erlotinib and enzastaurin in previously treated patients with advanced NSCLC and other advanced solid malignancies; secondary objectives included evaluation of the pharmacokinetic interaction between enzastaurin and erlotinib and the safety of the combination.

Methods

Eligibility criteria

Eligible patients included those with an incurable solid malignancy; no more than three prior systemic treatment regimens for advanced disease; an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2; an estimated life expectancy of at least 2 months; non-measurable or measurable disease defined by Response Evaluation Criteria in Solid Tumors (RECIST) [18]; adequate hematologic function including white blood cell count $\geq 3.0 \times 10^9$/L, absolute neutrophil count $\geq 1.5 \times 10^9$/L, platelet count $\geq 75.0 \times 10^9$/L, and hemoglobin ≥ 10.0 g/dL; adequate hepatic function including bilirubin ≤ 1.5 times the upper limit of normal (ULN) and alkaline phosphatase, aspartate transaminase, and alanine transaminase ≤ 2.5 times the ULN, or <5 times the ULN with liver metastases; and adequate renal function with serum creatinine ≤ 1.5 times the ULN. Patients who were unable to swallow tablets, unable to stop taking enzyme-inducing anti-epileptic drugs, or were previously treated with an EGFR inhibitor or enzastaurin were excluded from the study. Patients with symptomatic interstitial lung disease, a serious heart condition, second primary cancer, or who were pregnant or breast feeding were also excluded. Patients with central nervous system metastases were allowed only if they had completed local therapy and were off corticosteroids for at least 4 weeks. Prior chemotherapy or radiotherapy had to be completed at least 2 weeks before study enrollment and surgical intervention at least 4 weeks before enrollment.

The study protocol and informed consent were approved by the Stanford Institutional Review Board. All patients signed an informed consent document in compliance with the Declaration of Helsinki and good clinical practice guidelines.

Study design and treatment plan

This was a single-institution, open-label, non-randomized, phase I clinical trial that used a standard 3 + 3 dose-escalation model with two planned doses of enzastaurin.

Dose-limiting toxicity (DLT) was defined as the following events that occurred during cycle 1 according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 3.0): grade 4 hematologic events and grade 3 or 4 non-hematologic events except those that could be explained from a coexisting condition or events of nausea, vomiting, diarrhea, or skin rash that were controlled with supportive treatment.

All patients received oral enzastaurin (Eli Lilly and Company, Indianapolis, IN) and erlotinib (OSI, now Astellas/Genentech/Roche, Melville, NY) daily. Cycles were 28 days long. Enzastaurin was taken 30 min after a meal and erlotinib was taken 1 h before a meal in the first cycle; in subsequent cycles, erlotinib could be taken 2 h after a meal, as long as the timing of dosing was consistent. All cohorts received erlotinib 150 mg daily, the standard dose given as a single agent for advanced-stage NSCLC [10].

Cohort 1 was designed to include three patients at dose level 1: enzastaurin 250 mg daily with a loading dose of 500 mg on day 1 (given as 250 mg two times a day). All

three patients had to complete cycle 1 of dose level 1 without a DLT before enrolling an additional three patients at dose level 2, the full enzastaurin dose of 500 mg daily with a loading dose of 1125 mg on day 1 (given as 375 mg three times a day) [7]. If all three patients tolerated dose level 2 without a DLT, enrollment continued up to 12 patients at the maximum tolerated dose to complete the pharmacokinetic analysis and more fully explore the dose before initiating phase II. However, if one patient experienced a DLT at any dose level, the cohort was to be expanded to six patients. If no more than one patient within the expanded cohort of six patients experienced a DLT, the dose level could be escalated to the next higher dose. If two or more of the six patients experienced a DLT, the next lower dose level was the recommended dose. Patients continued study treatment until disease progression or unacceptable toxicity.

Treatment assessments

Patients were evaluated weekly for the first cycle and then every 28 days for subsequent cycles through a 30-day post-discontinuation period. Treatment compliance by pill count was performed at each visit, and adverse events (AEs) were monitored and graded before each cycle using the NCI-CTCAE version 3.0. AEs were reported regardless of relatedness to study treatment or procedure from the time of enrollment through the post-discontinuation period. At each visit, recording of patient's concomitant medications; physical examination; assessment of any AEs and ECOG performance status; and routine laboratory testing including complete blood count, chemistry, and coagulation studies were performed. Pre-treatment studies also included baseline imaging (computed tomography or magnetic resonance imaging) $\leq$28 days before enrollment. Although this study was not designed to assess efficacy, repeat imaging was performed and evaluated using RECIST every two cycles.

Pharmacokinetics

Blood samples for pharmacokinetic evaluations were collected at day 22 $\pm$ 3 days of cycle 1 for both enzastaurin and erlotinib. Plasma samples of 3 and 1 mL were used for enzastaurin (and its metabolite, LY326020) and for erlotinib, respectively. The collection times for enzastaurin were pre-dose and 2, 4, 6, and 8 h post-dose. The collection times for erlotinib were pre-dose and 2, 4, 6, and 10 h post-dose.

Pharmacokinetic parameters were computed using non-compartmental analysis using WinNonlin® Professional Edition version 5.0.1 (Pharsight, Mountain View, CA). The maximum steady-state plasma concentration ($C_{max,ss}$), time to maximum steady-state plasma concentration ($t_{max,ss}$), area under the concentration–time curve of the dosing interval ($AUC_{\tau,ss}$), and average steady-state concentration ($C_{av,ss}$) were calculated for enzastaurin, its metabolite (LY326020), and erlotinib. The apparent clearance of enzastaurin and erlotinib at steady state (CL_{ss}/F) was calculated as well as the metabolic ratio for LY326020, which was calculated using the ratio of the $AUC_{metabolite,ss}$ to $AUC_{parent,ss}$. Enzastaurin $C_{av,ss}$ and erlotinib CL_{ss}/F were compared with historical data [7, 19].

Results

Patients and treatment received

Sixteen patients were enrolled and treated in this study (median age of 64 years; range, 46–83 years) from May 2007 to June 2009 (Table 1). Most patients were female ($n = 13$) and Caucasian ($n = 11$). The majority ($n = 9$) had NSCLC and an ECOG performance status of 0 ($n = 5$) or 1 ($n = 10$), and patients had received one ($n = 5$), two ($n = 7$), or three ($n = 4$) prior chemotherapy regimens.

The majority of patients ($n = 15$) discontinued the study due to disease progression. One patient decided to stop therapy during cycle 2 for personal reasons. Fifteen patients completed at least two cycles of therapy. Four patients completed 12 cycles or more, with one patient

Table 1 Baseline patient demographics ($n = 16$)

Demographics	No. of patients
Sex	
Female	13
Male	3
Median age (range), years	64 (46–83)
Ethnicity	
Caucasian	11
East Asian	4
Hispanic	1
ECOG performance status	
0	5
1	10
2	1
Tumor type	
NSCLC	9
Sarcoma, GIST, parotid carcinoma, cholangiocarcinoma, biliary papillomatosis, thyroid cancer, HCC	7
Smoking history	
Yes (current/past)	8
No	8

ECOG Eastern Cooperative Oncology Group; *N* total population size; *NSCLC* non-small-cell lung cancer; *GIST* gastrointestinal stromal tumor; *HCC* hepatocellular carcinoma

receiving 14 cycles before developing progressive disease. The mean number of cycles received was 4.6 and the median was 2 (range, 1–14).

Recommended dose

Of three patients initially enrolled at dose level 1 (erlotinib 150 mg daily and enzastaurin 250 mg daily after the loading dose), one patient discontinued in cycle 1 due to rapid and fatal disease progression. This patient was replaced in the cohort. After no DLTs occurred in this cohort, dose level 2 was initiated and, as no DLTs occurred, a total of 12 patients were enrolled at dose level 2 as planned. Dose level 2 was the recommended phase II dose level (i.e., erlotinib 150 mg daily and enzastaurin 500 mg daily after the loading dose).

Safety and tolerability

AEs regardless of causality that occurred in ≥25% of patients are presented in Table 2. The most common AEs, regardless of relationship to treatment, were diarrhea, chromaturia, rash, decreased appetite, feces discoloration, and nausea. One patient in dose level 1 and 9 patients in dose level 2 experienced non-laboratory grade 3 or higher AEs possibly related to study drug. These AEs included anorexia, ataxia, diarrhea, diplopia, dizziness, pruritus, and vomiting (Table 3). No patient experienced grade 3–4 laboratory AEs possibly related to study drug. Serious AEs considered possibly drug-related were ataxia, diplopia, and drug interaction in one patient and balance disorder and fall in one patient. Other serious adverse events reported that were considered unrelated to treatment included one patient with a gastrointestinal stromal tumor who had a pulmonary embolism and deep vein thrombosis.

There were no deaths or discontinuations due to drug-related AEs while on study. Three deaths (one in dose level 1 and two in dose level 2) occurred within 30 days of discontinuation due to disease progression.

Table 2 Summary of all adverse events in ≥25% patients regardless of drug relatedness or grade ($N = 16$)

Preferred term	*n* (%)
Diarrhea	15 (93.8)
Chromaturia	12 (75.0)
Rash	11 (68.8)
Decreased appetite	9 (56.3)
Feces discolored	8 (50.0)
Nausea	8 (50.0)
Dyspnea	7 (43.8)
Fatigue	7 (43.8)
Pruritus	7 (43.8)
Dysgeusia	6 (37.5)
Abdominal pain	5 (31.3)
Back pain	5 (31.3)
Dry skin	5 (31.3)
Vomiting	5 (31.3)
Alopecia	4 (25.0)
Cough	4 (25.0)
Dermatitis acneiform	4 (25.0)
Dizziness	4 (25.0)
Epistaxis	4 (25.0)
Musculoskeletal pain	4 (25.0)

AEs with a start date during the study treatment period or within 30 days of the last dose. For patients reporting more than one occurrence of the same AE, the earliest occurrence of the worst severity was used for tabulation

AE adverse event; *N* total population size; *n* number of patients

Pharmacokinetics

The mean $C_{av,ss}$ at dose level 2 for enzastaurin and its active metabolite LY326020 was 750 nmol/L ($n = 12$) and 751 nmol/L ($n = 12$), respectively, after 22 days (±3 days) of 500-mg daily doses of enzastaurin with 150-mg daily doses of erlotinib.

The mean $AUC_{\tau,ss}$ was 18,000 nmol × h/L ($n = 12$) for both enzastaurin and its active metabolite LY326020 after 22 days (±3 days) of 500-mg daily doses of enzastaurin with 150-mg daily doses of erlotinib. The mean clearance (CL_{ss}/F) of enzastaurin was 53.8 L/h ($n = 12$). A summary of all steady-state pharmacokinetic parameters is shown in Table 4. The high variability for pharmacokinetic parameter estimates in the 250-mg dose group is due to a patient who had very high concentrations compared with the other two patients in the group.

The mean steady-state pharmacokinetic parameters for erlotinib 150 mg daily with 250- or 500-mg daily doses of enzastaurin are summarized in Table 5. The mean clearance (CL_{ss}/F) of erlotinib was 6.07 L/h when given with 250 mg of enzastaurin and 5.75 L/h when given with 500 mg of enzastaurin. Data from one patient in dose level 2 were excluded from the analysis due to an error in the dose record.

The mean steady-state plasma concentration–time profiles of erlotinib (after 150-mg daily doses with 250- or 500-mg daily doses of enzastaurin) and total analyte (enzastaurin + LY326020, following 250- or 500-mg daily doses of enzastaurin with 150 mg erlotinib) are shown in Fig. 1.

Response

Although the study was not designed to assess efficacy, there was one partial response (PR) in a patient with

Table 3 Summary of patients with non-laboratory CTCAE maximum grade 3 or 4 possibly related to study drug

CTCAE term, *n* (%)	Enzastaurin + erlotinib					
	Dose level 1 ($N = 4$)		Dose level 2 ($N = 12$)		Total ($N = 16$)	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Patients with at least one non-laboratory CTCAE	0	1 (25.0)	1 (8.3)	8 (66.7)	1 (6.3)	9 (56.3)
Anorexia	0	0	0	2 (16.7)	0	2 (12.5)
Ataxia	0	0	0	1 (8.3)	0	1 (6.3)
Diarrhea	0	0	2 (16.7)	2 (16.7)	2 (12.5)	2 (12.5)
Diplopia	0	0	0	1 (8.3)	0	1 (6.3)
Dizziness	0	0	1 (8.3)	0	1 (6.3)	0
Dry eye	0	0	0	1 (8.3)	0	1 (6.3)
Dry skin	0	0	0	1 (8.3)	0	1 (6.3)
Fatigue	0	0	1 (8.3)	0	1 (6.3)	0
GI—other	0	0	0	1 (8.3)	0	1 (6.3)
Hemorrhage, pulmonary, nose	0	0	0	1 (8.3)	0	1 (6.3)
Infection—other	0	0	0	1 (8.3)	0	1 (6.3)
Insomnia	0	0	0	1 (8.3)	0	1 (6.3)
Neurology—other	0	1 (25.0)	2 (16.7)	0	2 (12.5)	1 (6.3)
Ocular—other	0	0	0	1 (8.3)	0	1 (6.3)
Pain GI—abdomen NOS	0	1 (25.0)	0	0	0	1 (6.3)
Photosensitivity	0	1 (25.0)	0	0	0	1 (6.3)
Pruritus	0	1 (25.0)	0	1 (8.3)	0	2 (12.5)
Renal failure	0	0	1 (8.3)	0	1 (6.3)	0
Syncope	0	0	1 (8.3)	0	1 (6.3)	0
Vomiting	0	0	1 (8.3)	2 (16.7)	1 (6.3)	2 (12.5)
Watery eye	0	0	0	1 (8.3)	0	1 (6.3)

AEs with a start date during the study treatment period or within 30 days of the last dose. For patients reporting more than one occurrence of the same AE, the earliest occurrence of the worst severity was used for tabulation

CTCAE common terminology criteria for adverse events (version 3.0); *N* total population; *n* number of patients; *GI* gastrointestinal; *NOS* not otherwise specified

Table 4 Summary of enzastaurin steady-state plasma pharmacokinetic parameters following 250- or 500-mg once-daily doses of enzastaurin with 150-mg daily doses of erlotinib

	Geometric mean (CV%)					
	Enzastaurin		LY326020		Total analyte (enzastaurin + LY326020)	
	250 mg	500 mg	Enz 250 mg	Enz 500 mg	Enz 250 mg	Enz 500 mg
N	3	12	3	12	3	12
$C_{max,ss}$ (nmol/L)	618 (709)	1,600 (57)	431 (806)	980 (41)	978 (797)	2,620 (44)
$t^{a}_{max,ss}$ (h)	4.00 (4.00–6.00)	4.04 (4.00–8.00)	6.00 (0.00–6.00)	6.00 (4.00–8.00)	4.00 (4.00–6.00)	5.04 (4.00–8.00)
$AUC_{\tau,ss}$ (nmol × h/L)	6,590 (412)	18,000 (71)	7,100 (890)	18,000 (44)	14,000 (598)	37,100 (51)
$C_{av,ss}$ (nmol/L)	275 (412)	750 (71)	296 (890)	751 (44)	581 (598)	1,550 (51)
CL_{ss}/F (L/h)	73.6 (412)	53.8 (71)	NC (NC)	NC (NC)	NC (NC)	NC (NC)
MR	NC (NC)	NC (NC)	1.08 (52)	1.00 (55)	NC (NC)	NC (NC)

$AUC_{\tau,ss}$ area under the plasma concentration time–curve during one dosing interval at steady state; $C_{av,ss}$ average drug concentration under steady-state conditions during multiple dosing; CL_{ss}/F apparent clearance under steady-state conditions during multiple dosing; $C_{max,ss}$ maximum observed drug concentration during a dosing interval at steady state; *CV* coefficient of variation; *MR* metabolic ratio; *NC* non-calculable; $t_{max,ss}$ time of maximum observed drug concentration during a dosing interval at steady state

[a] Median (range)

Table 5 Summary of erlotinib steady-state plasma pharmacokinetic parameters following 150-mg daily doses of erlotinib with 250- or 500-mg once-daily doses of enzastaurin

	Geometric mean (CV%)	
	150 mg erlotinib	
	250 mg enzastaurin	500 mg enzastaurin
n	3	11
$C_{max,ss}$ (ng/mL)	1,460 (41)	1,570 (37)
$t^{a}_{max,ss}$ (h)	2.00 (2.00–6.02)	4.00 (2.00–6.00)
$AUC_{\tau,ss}$ (ng × h/mL)	24,700 (19)	26,100 (45)
$C_{av,ss}$ (ng/mL)	1,030 (19)	1,090 (45)
CL_{ss}/F (L/h)	6.07 (19)	5.75 (45)

$AUC_{\tau,ss}$ area under the plasma concentration–time curve during one dosing interval at steady state; $C_{av,ss}$ average drug concentration under steady-state conditions during multiple dosing; CL_{ss}/F apparent clearance under steady-state conditions during multiple dosing; $C_{max,ss}$ maximum observed drug concentration during a dosing interval at steady state; *CV* coefficient of variation; $t_{max,ss}$ time of maximum observed drug concentration during a dosing interval at steady state

[a] Median (range)

NSCLC that lasted for 12 cycles. This patient was an Asian female non-smoker, factors known to improve response to erlotinib [10], but her EGFR mutational status was not known. Three patients had stable disease (SD) for >12 months, including one patient with a decrease in tumor size of 27%. One of these patients was actively smoking during therapy, a factor known to decrease erlotinib exposure and efficacy [10]. All four patients with prolonged SD or PR had NSCLC and were female; two were Asian and two were Caucasian. Seven patients progressed after just two cycles, three other patients progressed before completing two cycles, and one progressed before completing one cycle. Of the seven patients who progressed by the first interim scan (after completion of two cycles), the majority had tumors other than NSCLC ($n = 4$) and were smokers.

Discussion

To our knowledge, this phase I clinical trial was the first to combine enzastaurin with an EGFR inhibitor. The combination showed good tolerability, with no DLTs, and some evidence of activity. We were able to safely administer the maximum doses of both drugs without unexpected toxicity or pharmacokinetic interactions. The recommended phase II dose of the combination is enzastaurin 500 mg orally daily, after a loading dose (1,125 mg on day 1 of cycle 1), and erlotinib 150 mg orally daily.

In our study, there were no unexpected AEs with the combination of erlotinib and enzastaurin, and those seen had been previously documented in single-agent studies of erlotinib or enzastaurin [8, 10]. The most common AEs in this study, regardless of relationship to therapy, were diarrhea, chromaturia, rash, decreased appetite, feces discoloration, and nausea. The most common possibly drug-related grade 3–4 toxicities included diarrhea, neurologic symptoms, and vomiting. In a phase II study of enzastaurin in advanced NSCLC, fatigue and nausea were the most common AEs [8]. Grade 3 toxicities in that study included ataxia, pulmonary embolism, and anemia in one patient each, and there were two study discontinuations, one due to grade 3 fatigue and one due to grade 1 dizziness [8]. In advanced NSCLC, the most common AEs of erlotinib alone include rash, diarrhea, anorexia, nausea, and fatigue [10]. In this trial, we did not see any additive toxicity and the regimen was well tolerated.

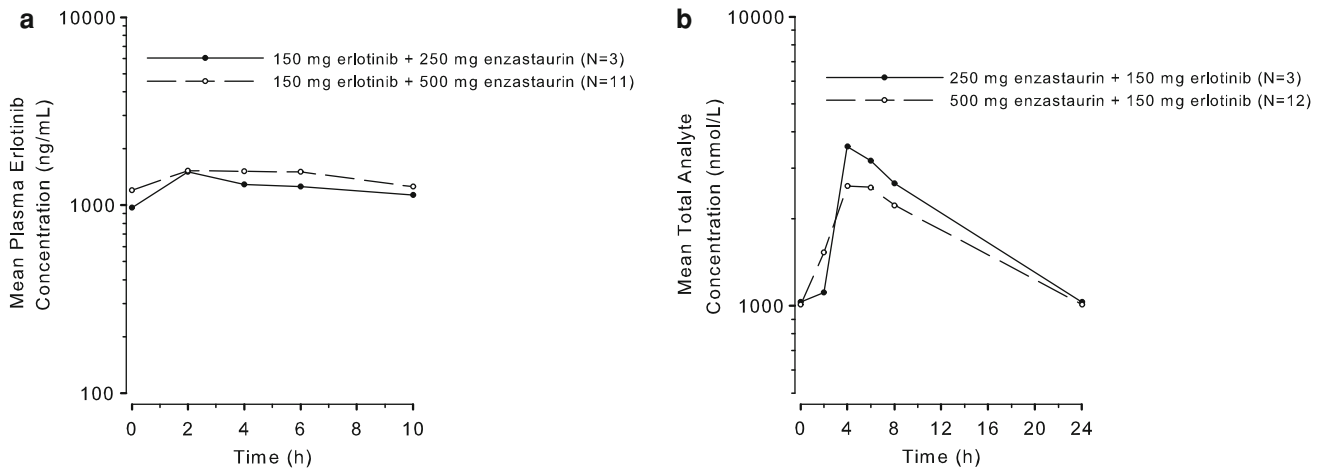

Fig. 1 Mean steady-state plasma concentration–time profiles of erlotinib (*left panel*, **a**) and total analyte (enzastaurin + LY326020; *right panel*, **b**)

The pharmacokinetic parameters of erlotinib appear similar when used in combination with 250- and 500-mg once-daily doses of enzastaurin. The steady-state clearance of erlotinib reported in a single-agent erlotinib study ranged from 4.36 to 6.27 L/h for doses that ranged from 50 to 200 mg [19]. In this study, steady-state clearance (CL_{ss}/F) of erlotinib was 6.07 and 5.75 L/h when given with 250- and 500-mg once-daily enzastaurin, respectively, which is within the range of values reported in the historical data.

The $AUC_{\tau,ss}$ of enzastaurin was 18,000 nmol × h/L in this study when enzastaurin 500 mg and erlotinib 150 mg were administered daily. This value is similar to the 23,600 nmol × h/L that was observed in the single-agent study of enzastaurin at 525 mg orally daily [7]. Likewise, in the current study, CL_{ss}/F was 53.8 L/h, which is not notably different from the CL_{ss}/F of 40.3 L/h in the previous study of single-agent enzastaurin at 525 mg orally daily [7]. Due to the high variability in CL_{ss}/F for both studies (CV% > 70), clearance does not appear to differ between the two studies, suggesting that erlotinib does not affect the pharmacokinetics of enzastaurin.

In this study, a PR was seen in one patient and prolonged SD was seen in three patients with NSCLC; thus, a phase II study of the combination in advanced NSCLC was initiated. The combination of erlotinib with other targeted agents, particularly anti-angiogenic agents, has been encouraging to date. For example, the combination of bevacizumab and erlotinib versus erlotinib and placebo at standard dosing in patients with advanced NSCLC who progressed after first-line chemotherapy ($n > 600$ patients) resulted in substantial improvements in median progression-free survival of 3.4 months versus 1.7 months ($P = 0.0001$) and overall response rates of 12.6% versus 6.2%, although no overall survival benefit was seen [20]. A randomized phase II study compared erlotinib plus bevacizumab or chemotherapy plus bevacizumab versus chemotherapy alone in patients with recurrent NSCLC and found the best survival in both bevacizumab arms, but the best tolerability in the erlotinib plus bevacizumab arm [21]. The addition of sorafenib, a multi-targeted tyrosine kinase inhibitor with activity against VEGF receptor, to erlotinib led to an increase in progression-free survival [22]. These combinations are also showing efficacy and tolerability in other cancers, such as a phase II trial of erlotinib plus bevacizumab in recurrent metastatic squamous cell carcinoma of the head and neck [23].

This study was conducted in multiple tumor types, but given the single-agent activity of erlotinib in NSCLC, further development of the combination will be in NSCLC. Although the study was not designed to assess efficacy, one of nine NSCLC patients in this study achieved a PR and four of the nine NSCLC patients were on therapy for a prolonged period of time (at least 12 cycles) with at least SD. Given the tolerable toxicity profile and the lack of pharmacokinetic interactions, the combination of erlotinib (150 mg orally daily) and enzastaurin (500 mg orally daily) was explored further. The phase II portion of this trial was initiated in patients with NSCLC who had previously been treated with one or two prior chemotherapy regimens but had no prior exposure to an EGFR-targeted agent.

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