Everolimus and Erlotinib as Second- or Third-Line Therapy in Patients with Advanced Non–Small-Cell Lung Cancer

Vassiliki A. Papadimitrakopoulou, MD, Jean-Charles Soria, MD, PhD,† Annette Jappe, RN,‡ Valentine Jehl, MSc,‡ Judith Klimovsky, MD,‡ and Bruce E. Johnson, MD§*

Introduction: The epidermal growth factor receptor inhibitor erlotinib is an approved treatment for chemotherapy-refractory advanced non–small-cell lung cancer (NSCLC). Because activated epidermal growth factor receptor signals through the phosphatidylinositol 3-kinase/Akt/mammalian target of rapamycin (mTOR) pathway, adding the oral mTOR inhibitor everolimus to erlotinib may improve efficacy by blocking multiple components of the same pathway. We conducted a phase I study to determine feasible dosages of combination therapy with erlotinib and everolimus for previously treated metastatic or unresectable NSCLC.

Methods: Participants had advanced NSCLC progressing after two or less previous chemotherapy regimens. Feasibility of daily/weekly everolimus plus daily erlotinib was determined using a *6 + 6* dose-escalation design based on the rate of dose-limiting toxicities. Antitumor activity was assessed by the Response Evaluation Criteria In Solid Tumors study.

Results: Of the 94 patients enrolled, 90% had stage IV NSCLC, 19% never smoked, and 15% were current smokers. Eighty-nine patients experienced one or more adverse events possibly related to any study medication. The most common dose-limiting toxicities were stomatitis (n = 5), rash (n = 4), and diarrhea (n = 3). Maximum tolerated doses were everolimus 5 mg per day or 50 mg per week plus erlotinib 150 mg per day. In daily everolimus cohorts (n = 74), nine patients achieved a complete/partial response and 28 had stable disease (median duration disease control, 9.3 months). In weekly everolimus cohorts (n = 20), no tumor response was observed; seven patients had stable disease (median duration, 9.6 months).

Conclusions: Combination therapy with everolimus 5 mg per day or 50 mg per week and erlotinib 150 mg per day provided acceptable tolerability and disease control. A randomized phase II study evaluating this combination in comparison with erlotinib alone is complete and is being analyzed.

Key Words: Dose-limiting toxicity, Erlotinib, Everolimus, Non–small-cell lung cancer, Phase I.

(*J Thorac Oncol.* 2012;7: 1594–1601)

Worldwide, lung cancer causes almost 1.4 million deaths each year, making it the most common cause of cancer death.[1] Approximately 85% of lung cancers are non–small-cell lung cancer (NSCLC).[2] The prognosis for patients with advanced NSCLC is generally poor; in the United States, the 5-year survival rate for patients with distant metastases was only 3.8% between 2001 and 2007.[3] Depending on the stage of the disease, current treatment options for NSCLC include surgery; radiotherapy; chemotherapy; and targeted therapies, including the antiangiogenic agent bevacizumab, the epidermal growth factor receptor (EGFR) inhibitors erlotinib, gefitinib, and cetuximab, and the anaplastic lymphoma kinase inhibitor crizotinib.[2,4–7] Erlotinib is an inhibitor of EGFR-associated tyrosine kinase activity. EGFR mediates cell proliferation, cell migration, and cell survival in lung cancer cells.[8] Administered orally once daily, erlotinib is currently the only EGFR inhibitor approved in the United States for the treatment of patients with previously treated, advanced NSCLC.[2] The use of erlotinib in treatment-refractory NSCLC is supported by the results of a phase III study that demonstrated significant prolongation of survival (compared with placebo) in patients with stage IIIb or IV NSCLC, whose disease progressed after platinum-based therapy.[9]

Whereas patients with wild-type *EGFR* derive limited benefit from treatment with EGFR inhibitors,[10] patients who carry activating mutations of *EGFR* show a high sensitivity to EGFR-targeted therapy, which correlates with dramatic clinical responses.[11,12] Because activated EGFR signals through the PI3K/Akt/mammalian target of rapamycin (mTOR) pathway,[13] one potential way to further improve the therapeutic efficacy of EGFR-targeted therapy in patients with wild-type EGFR receptors, where erlotinib has modest antitumor activity, is to combine an EGFR inhibitor with an mTOR inhibitor, thus blocking multiple components of the same signaling pathway.

*University of Texas, M.D. Anderson Cancer Center, Houston, Texas, †Gustave Roussy Institute and Paris University XI, Villejuif, France, ‡Novartis Pharmaceuticals Corporation, Basel, Switzerland and Florham Park, New Jersey, and §Dana-Farber Cancer Institute, Boston, Massachusetts.

Disclosure: A. Jappe, V. Jehl, and J. Klimovsky are employees of and hold stock in Novartis Pharmaceuticals. J.C. Soria has served as a consultant/advisory board member for Roche and Novartis. B.E. Johnson has served as a consultant/advisory board member (uncompensated) for AstraZeneca, Boehringer-Ingelheim, Genentech, KEW Group (Diagnostics), Millennium, and Pfizer; an immediate family member of Dr. Johnson holds stock in Celgene; Dr. Johnson has received remuneration for a patent reviewed for EGFR testing with Genzyme. V. Papadimitrakopoulou declares no conflicts of interest.

Address for correspondence: Vassiliki A. Papadimitrakopoulou, MD, University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Boulevard, Box 432, Houston, TX 77030. E-mail: vpapadim@mdanderson.org

ISSN: 1556-0864/12/0710-1594

Everolimus is an oral inhibitor of mTOR, a serine-threonine kinase that stimulates cell growth, proliferation, and angiogenesis in mammalian cells.[13] Everolimus is currently approved in the United States as anticancer therapy for the treatment of sunitinib- or sorafenib-refractory advanced renal cell carcinoma (RCC); progressive, unresectable, locally advanced or metastatic pancreatic neuroendocrine tumors (pNET); and subependymal giant cell astrocytoma associated with tuberous sclerosis that is not amenable to surgery.[14] Dysregulation of signal transduction via the PI3K/Akt/mTOR pathway has been implicated in the pathogenesis of NSCLC and the acquisition of resistance to chemo- and radiotherapy, as well as EGFR-targeted therapy.[15–17] Consistent with a possible role of the PI3K/A kt/mTOR pathway in NSCLC, everolimus administered at 10 mg per day showed modest antitumor activity (4.7% response rate and 47% disease-control rate at 8 weeks) in 85 patients with NSCLC previously treated with chemotherapy alone or chemotherapy plus an EGFR inhibitor.[18] Results of preclinical studies further suggest that the combination of an mTOR inhibitor and erlotinib may have synergistic antitumor activity in NSCLC.[19,20] Thus, there is adequate evidence to test the hypothesis that everolimus plus erlotinib might provide greater therapeutic benefits than erlotinib monotherapy in previously treated patients with advanced NSCLC.

The primary objective of this study was to assess the feasibility of different doses and dose schedules of everolimus and erlotinib for second- and third-line combination therapy in patients with metastatic NSCLC. Both daily and weekly dosing schedules of everolimus were investigated because previous pharmacodynamic studies in advanced solid tumors indicated that inhibition of mTOR signaling and antitumor activity were observed with both dosing schedules.[21–23] Starting doses for both drugs were based on experience from previous clinical studies that evaluated the safety and efficacy of everolimus or erlotinib in this patient population.[9,18] Both daily and weekly everolimus dosing were explored to identify the optimal schedule in terms of pharmacokinetics and tolerability.

PATIENTS AND METHODS

Patients

Study participants were aged 18 years or olderand had advanced, pathologically confirmed NSCLC that showed progression on serial computed tomography scans despite one or two previous chemotherapy regimens, at least one of which included cisplatin or carboplatin. Additional inclusion criteria were a World Health Organization performance status of 2 or less and adequate bone marrow and hepatic function. Both smokers and nonsmokers (defined as patients who smoked fewer than 100 cigarettes in a lifetime) were included in the study. Patients previously treated with an EGFR inhibitor or requiring concurrent treatment with an agent also used in the treatment of cancer, receiving chronic therapy with steroids or immunosuppressive agents, or who had received another investigational agent in the previous 4 weeks were excluded. Other exclusion criteria were leptomeningeal or uncontrolled brain metastases, malignancies other than lung cancer in the previous 2 years (except for adequately treated cervical carcinoma, basal cell carcinoma, or squamous cell carcinoma), evidence of human immunodeficiency virus infection, impairment of gastrointestinal function that may significantly alter absorption of a study drug, and any concurrent severe or uncontrolled disease that could compromise study participation. All patients provided written informed consent. The study protocol was approved by the Institutional Review Boards of all institutions, and the study was conducted in accordance with the principles of the Declaration of Helsinki and amendments concerning medical research in humans.

Study Design and Treatments

This phase I study was a multicenter, open-label, nonrandomized, sequential dose-escalation study. The study assessed the dose-limiting toxicities (DLTs) of daily and weekly doses of oral everolimus in combination with daily oral erlotinib in previously treated patients with advanced NSCLC to determine the feasible dose and schedule of combination therapy. Patients were enrolled in groups of six per dose cohort, with enrollment alternating between daily and weekly cohorts. Once the maximum tolerated dose (MTD) for a given schedule was determined, enrollment in that schedule was stopped. Dose-escalation decisions were as follows: If two of six patients in any dose cohort experienced a DLT, six additional patients were enrolled in the same cohort. The dose of everolimus or erlotinib was escalated if one or no DLT was observed in six patients or if three or fewer DLTs were observed in 12 patients. If four or more DLTs were observed in 12 patients of any cohort, an additional six patients were enrolled at the previous dose level (up to 12 in total); if 12 patients were already enrolled at the lower dose level, this level was declared the MTD. At all decision-making time points, the clinical opinion of the investigators was considered together with the dose-escalation criteria.

Starting doses for the daily and weekly everolimus schedules were everolimus 2.5 mg per day plus erlotinib 100 mg per day and everolimus 30 mg per week plus erlotinib 150 mg per day. The planned everolimus doses were 5 mg every other day (replaced by 2.5 mg/day after an interim pharmacokinetic assessment), 5 mg per day, 10 mg per day, 20 mg per week, 30 mg per week, and 50 mg per week. The planned erlotinib doses were 50 mg per day, 75 mg per day, 100 mg per day, and 150 mg per day. In all cohorts, patients received a single dose of erlotinib on day 1, followed by a 24-hour concentration profile. Treatment was withheld until day 8, at which point erlotinib and everolimus were initiated according to the dose and schedule specified by the dose-escalation scheme. Partially overlapping toxicities were anticipated to be more severe with the full dose of erlotinib recommended as a single agent for relapsed NSCLC (150 mg/day) and the 10 mg per day dose of everolimus approved for advanced RCC and progressive, advanced pNET.

The following adverse events were considered to be DLTs if they occurred in the first cumulative 28 days of combined treatment and were suspected to be related to a study drug: grade 3 or 4 nonhematologic toxicity (except hypercholesterolemia, hypertriglyceridemia, or hyperglycemia) despite

appropriate therapy or grade 3 or 4 neutropenia or thrombocytopenia. After the three cohorts completed the daily dosing regimen, mucositis that rapidly resolved after treatment interruption was observed as the predominant DLT; therefore, the nonhematologic DLT criteria were modified and redefined as grade 3 nonhematologic toxicity (except hypercholesterolemia, hypertriglyceridemia, or hyperglycemia) that did not resolve to grade 2 or lower within 7 days of treatment interruption or that, despite appropriate therapy, recurred after treatment interruption within the first cumulative 28 days of combined treatment; other DLT criteria remained the same.

Assessments and Analyses

Safety evaluations included continuous monitoring of adverse events and regular assessment of vital signs, physical condition, and clinical laboratory tests. Adverse events were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.[24] The safety population included all patients who received one or more dose of the study drug and had a postbaseline safety assessment. The MTD-determining population included all patients who received 28 or more cumulative days of combination treatment with everolimus and erlotinib and completed all required safety evaluations or who experienced a DLT within 28 days of combination treatment with everolimus and erlotinib.

Tumor assessments were performed by computed tomography scans every 4 weeks for the first 16 weeks after the first combined administration of everolimus and erlotinib and every 8 weeks thereafter. Tumor response was assessed within 7 days of the scheduled date according to the Response Evaluation Criteria In Solid Tumors.[25] Efficacy was assessed in the full analysis set, defined as all patients who received one or more doses of any study drug, and the per-protocol population, defined as all patients who received one or more doses of any study drug and had a baseline assessment and one or more postbaseline tumor assessments after 5 weeks.

Blood samples for pharmacokinetic analysis of the daily everolimus schedule were collected predose and 1, 2, 5, 8, and 24 hours postdose on days 8 and 22; samples for analysis of the weekly everolimus schedule were collected predose on day 8 and 1, 2, 4, 24, and 168 hours postdose. Regardless of the everolimus schedule, blood samples for the evaluation of erlotinib were collected predose and 1, 3, 5, 8, and 24 hours postdose on days 1, 8, and 22. Trough levels for daily and weekly everolimus and daily erlotinib were evaluated once a month from week 8 until month 4. An additional blood trough level evaluation for the weekly everolimus cohort was performed predose on day 22. Blood samples were collected by direct venipuncture or an indwelling cannula in a forearm vein into a tube containing ethylenediaminetetraacetic acid (for everolimus) or heparin (for erlotinib). Everolimus samples were frozen at or below −20°C until shipment to Novartis Bioanalytics (Rueil-Malmaison, France) and WuXi Apptec (Shanghai, China) for analysis. Erlotinib samples were frozen at or below –20°C until shipment to MDS Laboratorie (Zurich, Switzerland) for analysis. Concentrations of everolimus and erlotinib and its primary metabolite, OSI-420, were determined using validated methods. In brief, everolimus concentrations were determined from 2-ml whole blood samples by a liquid chromatography/mass spectrometry method with a lower limit of quantification of 0.3 ng/ml. Erlotinib and OSI-420 concentrations were determined from 3-ml plasma samples after liquid/liquid extraction using a high-performance liquid chromatograph equipped with an AB/MDS Sciex 4000 mass spectrometer; the lower limit of quantification for erlotinib and OSI-420 was 1.00 ng/ml each. The pharmacokinetic parameters of the maximum concentration (C_{max}), time to reach C_{max} (t_{max}), the trough concentration (C_{min}), and the area under the curve (AUC) over the dosing interval ($AUC_{0–tlast}$) or to time infinity ($AUC_{0–inf}$) were derived by noncompartmental analysis using WinNonlin version 5.2 (Pharsight, Mountain View, CA). The effect of coadministration of everolimus and erlotinib (day 8) on the pharmacokinetics of erlotinib was assessed in the MTD-determining population by calculating the geometric mean and 90% confidence interval for the ratio of C_{max} and AUC of erlotinib plus everolimus to erlotinib alone.

RESULTS

Patients

A total of 94 patients were enrolled in the study from June 14, 2005 to May 1, 2008. On the basis of dose-escalation criteria for determining the MTD, 74 patients were enrolled in the daily dose cohorts and 20 patients in the weekly dose cohorts (Table 1). All patients were evaluated for safety, including two patients who did not receive everolimus treatment (1 in the everolimus 5 mg/day plus erlotinib 100 mg/day cohort; 1 in the everolimus 50 mg/week plus erlotinib 150 mg/day cohort). The majority of study participants were white, 56% were men, and the median age was 60 years. Fewer than 20% of the participants had never smoked, and 15% were smokers within 12 months before the start of or when entering the study. Most patients (68%) had adenocarcinomas. Ninety percent of the patients had stage IV NSCLC, and two thirds had a World Health Organization performance status of 1 (Table 1). By December 17, 2009, all but three patients had discontinued study participation; there was only one reported death at this time. Most participants discontinued because of disease progression (65%) or adverse events (26%); others discontinued because of withdrawal of consent (4%), abnormal laboratory test results (1%), or death (1%).

Treatment Exposure and Dose Reductions

Patient exposure to everolimus/erlotinib combination therapy is shown in Table 2. Patients who were assigned to receive everolimus 5 mg per day plus erlotinib 100 mg per day had the longest exposure, with a median of 3.5 months (range, 0.2–25.8) and a mean of 6.7 months (standard deviation, 7.66). Overall, the median duration of exposure for the weekly cohorts was shorter than that of the daily cohorts (Table 2). Among the daily dose cohorts, patients treated with everolimus 5 mg plus erlotinib 150 mg experienced the least dose reductions or treatment interruptions (25%; 2 of 8 patients) for each drug. Among weekly dose cohorts, no patients receiving everolimus 30 mg plus erlotinib 150 mg

TABLE 1. Patient Demographic and Baseline Characteristics (Full Analysis Set)

Variable	Daily Cohorts *n* = 74	Weekly Cohorts *n* = 20	Total N = 94
Age, yrs			
Male, mean ± SD	61 ± 9.5	59 ± 9.0	61 ± 9.4s
Male, median (range)	61 (35 − 77)	58 (46 − 77)	60 (35 − 77)
Sex, *n* (%)			
Male	40 (54.1)	13 (65.0)	53 (56.4)
Female	34 (45.9)	7 (35.0)	41 (43.6)
Race, *n* (%)			
White	69 (93.2)	19 (95.0)	88 (93.6)
Black	1 (1.4)	0	1 (1.1)
Asian	3 (4.1)	0	3 (3.2)
Other	1 (1.4)	1 (5.0)	2 (2.1)
Smoking history			
Never smoked,[a] *n* (%)	14 (18.9)	4 (20.0)	18 (19.1)
Male; female (*n*)	6; 8	2; 2	8; 10
Ever smoked,[b] *n* (%)	60 (81.1)	16 (80.0)	76 (80.9)
Male; female (*n*)	34; 26	11; 5	45; 31
Current smoker,[c] *n* (%)	10 (13.5)	4 (20.0)	14 (14.9)
Male; female (*n*)	5; 5	3; 1	8; 6
Tumor histology, *n* (%)			
Adenocarcinoma	50 (67.6)	14 (70.0)	64 (68.1)
Squamous cell carcinoma	8 (10.8)	2 (10.0)	10 (10.6)
Large cell carcinoma	5 (6.8)	3 (15.0)	8 (8.5)
Bronchioalveolar carcinoma	1 (1.4)	0	1 (1.1)
Other	10 (13.5)	1 (5.0)	11 (11.7)
WHO performance status, *n* (%)			
0	19 (25.7)	6 (30.0)	25 (26.6)
1	49 (66.2)	14 (70.0)	63 (67.0)
2	6 (8.1)	0	6 (6.4)
Cancer stage, *n* (%)			
III, IIIb	8 (10.8)	1 (5.0)	9 (9.6)
IV, Iva	66 (89.2)	19 (95.0)	85 (90.4)
Previous antineoplastic therapy, *n* (%)	74 (100)	20 (100)	94 (100)
Chemotherapy	74 (100)	20 (100)	94 (100)
One regimen	45 (60.8)	11 (55.0)	56 (59.6)
Two regimens	29 (39.2)	9 (45.0)	38 (40.4)
Immunotherapy	0	1 (5.0)	1 (1.1)
Targeted therapy	23 (31.1)	7 (35.0)	30 (31.9)
Other	3 (4.1)	0	3 (3.2)

[a]Defined as smoking < 100 cigarettes in lifetime.
[b]Defined as smoking > 100 cigarettes in lifetime.
[c]Defined as smoking cigarettes within 12 months before the start of or when entering the study.
WHO, World Health Organization.

had dose reductions or interruptions of everolimus. Dose reductions or interruptions in all other daily and weekly dose cohorts ranged from 29% to 50% for each drug and were most commonly caused by adverse events.

Dose-Limiting Toxicities and Safety

A total of 15 patients (20%) in the six daily everolimus cohorts and three patients (15%) in the 2 weekly everolimus cohorts experienced DLTs (Table 3). The most common individual DLTs were stomatitis (*n* = 5), rash (*n* = 4), and diarrhea (*n* = 3). Only one patient experienced a hematologic DLT (neutropenia). On the basis of the prespecified DLT criteria and the clinical opinion of the investigators, the feasible MTDs identified were everolimus 5 mg per day plus erlotinib 150 mg per day and everolimus 50 mg per week plus erlotinib 150 mg per day, respectively.

Of the 94 study participants, 89 (95%) experienced one or more adverse events suspected to be related to everolimus and/or erlotinib. Forty patients (43%) experienced possibe drug-related grade 3 or 4 events during treatment; the most common were stomatitis (*n* = 12), rash (*n* = 5), and diarrhea (*n* = 11). All other possible drug-related grade 3 or 4 events that occurred in more than one patient are listed in Table 4. Serious adverse events occurred in 51 patients (54%), most commonly gastrointestinal disorders (*n* = 13), infections and infestations (*n* = 11), and respiratory disorders (*n* = 10). One patient died of acute myocardial infarction after 890 days of therapy with everolimus 2.5 mg per day plus erlotinib 100 mg per day; the death was not suspected to be related to the study drug.

Disease Control

In the full analysis set (N = 94), disease control was achieved by 44 patients (47%), with one patient (1%) achieving a complete response (CR), eight patients (9%) achieving a partial response (PR), and 35 patients (37%) achieving stable disease as best overall response (Table 5). The one CR and the eight PRs occurred in the daily cohort. The median duration of disease control was 9.3 months in the daily dose cohorts (*n* = 74) and 9.6 months in the weekly dose cohorts (*n* = 20). Of the 74 patients enrolled in the daily dose cohorts, 48 patients composed the per-protocol population; disease control was achieved by 35 (73%) of these patients, with one (1%) achieving a CR and eight (11%) achieving a PR as best overall response, and 26 (54%) with stable disease (Table 5). Of the nine responders, five were men, four had a history of smoking (including 1 current smoker), seven had adenocarcinomas, one had squamous cell carcinoma, and one had NSCLC of other histology. Of 20 patients enrolled in the weekly dose cohorts, 14 composed the per-protocol population; disease control was achieved by seven (50%) of these patients, all of whom achieved stable disease as best overall response (Table 5). In the per-protocol population, progressive disease as the best overall response occurred in 12 patients (25%) in the daily dose cohorts and five patients (36%) in the weekly cohorts.

Pharmacokinetics

The pharmacokinetic parameters of everolimus, erlotinib, and its principle metabolite OSI-420 were evaluated at all doses investigated in this study (data not shown). On the basis of the ratio of geometric means and accompanying 90% confidence intervals for the C_{max}, $AUC_{0–tlast}$, and $AUC_{0–inf}$, of erlotinib and OSI-420, everolimus did not significantly influence the

TABLE 2. Exposure to Everolimus/Erlotinib Combination Therapy (Safety Population)

	Daily Cohorts						Weekly Cohorts	
Duration, months	**5/100 *n* = 15**	**5 EOD/100 *n* = 12**	**2.5/100 *n* = 13**	**2.5/150 *n* = 13**	**5/75 *n* = 13**	**5/150 *n* = 8**	**30/150 *n* = 6**	**50/150 *n* = 14**
Mean ± SD	6.7 ± 7.66	4.7 ± 4.37	6.1 ± 9.62	4.9 ± 7.43	2.6 ± 3.52	4.4 ± 6.62	1.6 ± 0.54	4.1 ± 8.11
Median	3.5	3.1	1.9	2.5	0.7	1.5	1.7	0.9
Range	0.2–25.8	0.3–12.9	0.5–29.0	0.2–27.6	0.3–11.1	0.2–19.8	0.9–2.3	0.2–29.7

All doses are listed as mg of everolimus/mg of erlotinib.
EOD, every other day.

TABLE 3. Dose-Limiting Toxicities (Safety Population)

	Daily Cohorts, *n*							Weekly Cohorts, *n*			
System Organ Class/ Preferred Term	**5/100 *n* = 15**	**5 EOD/100 *n* = 12**	**2.5/100 *n* = 13**	**2.5/150 *n* = 13**	**5/75 *n* = 13**	**5/150 *n* = 8**	**Total Daily, *n* (%) *n* = 74**	**30/150 *n* = 6**	**50/150 *n* = 14**	**Total Weekly, *n* (%) *n* = 20**	**Total, N N = 94**
Total patients with dose-limiting toxicities	2	3	4	2	3	1	15 (20.3)	1	2	3 (15.0)	18 (19.1)
Blood and lymphatic system disorders											
Neutropenia	0	0	1	0	0	0	1 (1.4)	0	0	0	1 (1.1)
Gastrointestinal disorders, metabolism, and nutrition disorders											
Diarrhea	0	2	0	0	1	0	3 (4.1)	0	0	0	3 (3.2)
Dysphagia	1	0	0	0	0	0	1 (1.4)	0	0	0	1 (1.1)
Nausea	0	0	0	0	1	0	1 (1.4)	0	0	0	1 (1.1)
Stomatitis	1	1	2	0	1	0	5 (6.8)	0	0	0	5 (5.3)
Vomiting	0	0	0	0	1	0	1 (1.4)	0	0	0	1 (1.1)
Infections and infestations											
Dermatitis infected	0	0	0	0	0	1	1 (1.4)	0	0	0	1 (1.1)
Skin infection	0	0	0	0	0	1	1 (1.4)	0	0	0	1 (1.1)
Skin and subcutaneous disorders											
Dermatitis acneiform	0	0	0	0	0	0	0	0	2	2 (10.0)	2 (2.1)
Dry skin	0	0	0	0	1	0	1 (1.4)	0	0	0	1 (1.1)
Palmar-plantar erythrodysesthesia	0	0	0	1	0	0	1 (1.4)	0	0	0	1 (1.1)
Rash	0	1	1	1	0	0	3 (4.1)	1	0	1 (5.0)	4 (4.3)

All doses are listed as mg of everolimus/mg of erlotinib.
EOD, every other day.

pharmacokinetics of erlotinib or OSI-420 (Table 6). Similarly, erlotinib did not influence the pharmacokinetics of everolimus (data not shown).

DISCUSSION

This is the first report of a clinical study evaluating the safety and antitumor activity of an mTOR inhibitor in combination with erlotinib in previously treated patients with advanced NSCLC. The results of this study suggest that based on tolerability, the administration of everolimus 5 mg day combined with erlotinib 150 mg per day or everolimus 50 mg per week combined with erlotinib 150 mg per day constitutes a feasible combination therapy for this patient group. Moreover, clinical responses and disease-control rates suggestive of antitumor activity of everolimus plus erlotinib were observed in all daily cohorts in this study. Everolimus 5 mg per day combined with erlotinib 150 mg per day, which corresponds to one-half of the everolimus dose recommended for patients with RCC and pNET and the full recommended dose for erlotinib, was evaluated in the phase II portion of this study (data analysis underway). The choice of the daily dosing regimen was based on the results of previous pharmacodynamics studies that showed that daily everolimus administration may ensure more profound inhibition of the mTOR pathway than weekly administration.[22,23]

Observations from clinical studies indicate that everolimus and erlotinib have overlapping and potentially additive adverse-events profiles, with both drugs exhibiting tendencies to cause stomatitis, rash, and diarrhea.[9,18,21,26,27] Consistent with these observations, the present study found stomatitis,

TABLE 4. Grade 3 or 4 Adverse Events with Suspected Relationship to Study Drugs in More Than One Patient (Safety Population)

	Daily Cohorts, *n*							Weekly Cohorts, *n*			
System Organ Class/Preferred Term, *n*	**5/100 *n* = 15**	**5 EOD/100 *n* = 12**	**2.5/100 *n* = 13**	**2.5/150 *n* = 13**	**5/75 *n* = 13**	**5/150 *n* = 8**	**Total Daily, *n* (%) *n* = 74**	**30/150 *n* = 6**	**50/150 *n* = 14**	**Total Weekly, *n* (%) *n* = 20**	**Total, *n* (%) N = 94**
Blood and lymphatic system disorders											
Anemia	0	0	0	0	2	0	2 (2.7)	0	0	0	2 (2.1)
Neutropenia	0	0	1	0	0	0	1 (1.4)	0	1	1 (5.0)	2 (2.1)
Gastrointestinal disorders, metabolism and nutrition disorders											
Diarrhea	2	3	0	3	2	1	11 (14.9)	0	0	0	11 (11.7)
Stomatitis	3	1	2	1	2	1	10 (13.5)	1	1	2 (10.0)	12 (12.8)
Skin and subcutaneous tissue disorders											
Dermatitis acneiform	0	0	0	0	0	0	0	0	2	2 (10.0)	2 (2.1)
Palmar-plantar erythrodysesthesia syndrome	0	0	0	1	0	1	2 (2.7)	0	0	0	2 (2.1)
Rash	1	1	1	1	0	0	4 (5.4)	1	0	1 (5.0)	5 (5.3)
Other disorders											
Alanine aminotransferase increased	0	0	0	1	1	0	2 (2.7)	0	0	0	2 (2.1)
Dehydration	0	0	0	0	2	0	2 (2.7)	1	0	1 (5.0)	3 (3.2)
Hypokalemia	0	0	0	0	1	0	1 (1.4)	0	1	1 (5.0)	2 (2.1)

All doses are listed as mg of everolimus/mg of erlotinib. A patient with multiple occurrences of a single adverse event is counted only once in that adverse event category.
EOD, every other day.

TABLE 5. Best Overall Response

	Daily Cohorts, *n*							Weekly Cohorts, *n*			
	5/100	**5 EOD/100**	**2.5/100**	**2.5/150**	**5/75**	**5/150**	**Total Daily, *n* (%)**	**30/150**	**50/150**	**Total Weekly, *n* (%)**	**Total, *n* (%)**
Full analysis set, *n*	15	12	13	13	13	8	74	6	14	20	94
CR	0	0	1	0	0	0	1 (1.4)	0	0	0	1 (1.1)
PR	1	2	1	3	1	0	8 (10.8)	0	0	0	8 (8.5)
SD	9	4	6	4	2	3	28 (37.8)	3	4	7 (35.0)	35 (37.2)
PD	3	3	5	4	8	4	27 (36.5)	3	5	8 (40.0)	35 (37.2)
Unknown	2	3	0	2	2	1	10 (13.5)	0	5	5 (25.0)	15 (16.0)
Disease control (CR, PR, or SD)	10	6	8	7	3	3	37 (50.0)	3	4	7 (35.0)	44 (46.8)
Per-protocol population, *n*	10	9	9	8	7	5	48	5	9	14	62
CR	0	0	1	0	0	0	1 (2.1)	0	0	0	1 (1.6)
PR	1	2	1	3	1	0	8 (16.7)	0	0	0	8 (12.9)
SD	9	4	5	3	2	3	26 (54.2)	3	4	7 (50.0)	33 (53.2)
PD	0	2	2	2	4	2	12 (25.0)	2	3	5 (35.7)	17 (27.4)
Unknown	0	1	0	0	0	0	1 (2.1)	0	2	2 (14.3)	3 (4.8)
Disease control (CR, PR, or SD)	10	6	7	6	3	3	35 (72.9)	3	4	7 (50.0)	42 (67.7)

All doses are listed as mg of everolimus/mg of erlotinib.
EOD, every other day; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

rash, and diarrhea to be the predominant grade 3 or 4 adverse events suspected to be related to treatment, and the predominant DLTs. Results of a phase III study of erlotinib in patients with previously treated, advanced NSCLC showed that daily administration of 150 mg erlotinib provided significant survival benefits compared with best standard care (6.7 months versus. 4.7 months), but also led to treatment discontinuation by 5% of the patients who received erlotinib.[9] This rate of discontinuation is comparable to that reported in other studies of erlotinib monotherapy in patients with advanced NSCLC.[28] In

TABLE 6. Ratio of Geometric Means and 90% Confidence Intervals for Pharmacokinetic Parameters of Erlotinib and OSI-420 (Safety Population)

	Daily Cohorts							Weekly Cohorts	
	Postamendment		Postamendment					Preamendment	
Parameter	**5/100**	**5 EOD/100**	**5/100**	**2.5/100**	**2.5/150**	**5/75**	**5/150**	**30/150**	**50/150**
Erlotinib									
C_{max}, ng/ml	n[a]	5/5	11/10	7/8	12/11	12/12	7/6	5/6	10/11
	GMR (90% CI)	1.046 (0.676–1.617)	1.232 (0.976–1.554)	0.974 (0.579–1.638)	0.923 (0.739–1.153)	1.123 (0.888–1.419)	1.297 (0.885–1.900)	0.989 (0.738–1.325)	1.172 (0.922–1.490)
$AUC_{0-tlast}$, ng·h/ml	n[a]	5/0	9/0	5/4	10/9	9/9	5/5	5/5	7/8
	GMR (90% CI)	NA	NA	0.858 (0.473–1.556)	0.951 (0.830–1.089)	1.184 (0.942–1.488)	1.347 (0.775–2.343)	0.820 (0.620–1.083)	1.278 (0.989–1.651)
AUC_{0-inf}, ng·h/ml	n	5/2	9/8	5/4	10/10	9/9	5/5	5/5	7/8
	GMR (90% CI)	3.139 (0.576–17.120)	1.652 (0.573–4.760)	0.714 (0.509–1.002)	1.030 (0.824–1.287)	1.347 (1.059–1.714)	1.413 (0.805–2.482)	0.781 (0.294–2.077)	1.302 (1.142–1.485)
OSI-420									
C_{max}, ng/ml	n[a]	5/5	10/8	7/8	10/11	11/10	6/8	5/5	10/11
	GMR (90% CI)	0.987 (0.665–1.465)	1.054 (0.762–1.458)	1.135 (0.679–1.897)	1.017 (0.622–1.662)	1.139 (0.778–1.668)	1.451 (1.228–1.714)	1.059 (0.697–1.611)	1.046 (0.788–1.390)
$AUC_{0-tlast}$, ng·h/ml	n[a]	2/0	90/	5/6	9/9	9/9	4/4	5/3	7/8
	GMR (90% CI)	NA	NA	1.011 (0.682–1.499)	1.153 (0.665–2.000)	1.307 (0.932–1.833)	1.699 (0.819–3.525)	0.867 (0.545–1.381)	1.264 (0.919–1.739)
AUC_{0-inf}, ng·h/ml	n[a]	3/2	9/8	5/6	10/9	9/8	4/4	5/3	7/8
	GMR (90% CI)	1.880 (NA)	2.011 (1.083–3.734)	1.173 (0.451–3.050)	1.466 (0.809–2.655)	1.578 (0.958–2.599)	1.681 (0.705–4.009)	0.783 (0.530–1.155)	1.252 (1.112–1.410)

All doses are listed as mg of everolimus/mg of erlotinib.

[a]Presented as number of samples available for erlotinib plus everolimus/number of samples available for erlotinib alone.

GMR presented as geometric mean of erlotinib plus everolimus to geometric mean of erlotinib alone. Geometric means were obtained by back-transforming the mean of the log-transformed parameter on the original scale.

The log-transformed pharmacokinetic parameter is modeled by means of a linear model adjusted for the profile day as a fixed effect and the patient as a random effect.

EOD, every other day; GMR, geometric mean ratio; NA, not available.

the present study, 26% of the patients discontinued treatment because of adverse events. Therefore, dose reduction or temporary interruption of therapy may be needed for patients who cannot tolerate the daily combination regimen of everolimus 5 mg plus erlotinib 150 mg. Antitumor activity was observed more consistently with daily dosing of everolimus; everolimus doses were interrupted and adjusted during the trial to administer erlotinib at the dose approved by the U.S. Food and Drug Administration. This large sample provided the investigators with substantial confidence and experience with the chosen phase II dosing schedule.

Preliminary disease-control rates observed in the current study with erlotinib and everolimus combination therapy seems to compare favorably to that reported in previous clinical studies of erlotinib or everolimus monotherapy as second- or third-line therapy for advanced NSCLC.[9,18] In the current study, patients in the daily everolimus cohorts achieved a disease-control rate of 50% (37 of 74) in the full analysis set (73% in the per-protocol population), with nine of 74 patients (12%) (19% in the per-protocol population) experiencing a CR or PR as the best overall response; median duration of stable disease was 9.3 months. In the weekly everolimus cohorts, seven of 20 patients (35%) in the full analysis set (50% in the per-protocol population) had stable disease as the best overall response, with a median duration of 9.6 months. In comparison, a phase III study of erlotinib conducted in 427 patients with previously treated advanced NSCLC resulted in 8.9% of erlotinib recipients achieving a CR or PR and 45% achieving disease control; the median duration of response was 7.9 months with erlotinib alone.[9] In a phase II study of everolimus 10 mg daily in 85 patients with previously treated, advanced NSCLC, 4.7% of patients achieved a PR, and disease control was achieved in 47% of patients.[18] Data on the feasibility of combination therapy with everolimus and the EGFR inhibitor gefitinib are also available. In a phase I study of 10 patients with previously treated, advanced NSCLC, two patients achieved a PR that was maintained for 4 months in one patient and 5 months in the other. Of note, neither of these patients demonstrated *EGFR* mutations previously associated with gefitinib response.[29] In the cohort of 31 patients with previously treated disease enrolled in a phase II study of everolimus 5 mg per day plus gefitinib 250 mg per day, three (9.7%) experienced a PR and 17 (54.8%) achieved stable disease that lasted for a median of 3 months; in this phase II study, one of the three patients who experienced a PR had an *EGFR*-activating mutation.[30] Although interpretation of the efficacy results of the present study is limited by the lack of *EGFR* mutation status from tumors of responding patients, the results in this molecularly unselected population suggest that combination treatment with erlotinib and everolimus may be superior to treatment with erlotinib alone.

Few treatment options are available for patients with advanced NSCLC whose first- or second-line therapy fails.[2,4,7,31] Currently, erlotinib is the only treatment recommended by professional oncology societies in the United States and Europe as third-line therapy for patients with stage IV NSCLC.[2,4,7] The present phase I trial demonstrated that the combination of everolimus 5 mg per day or 50 mg per week and erlotinib 150 mg per day had acceptable tolerability in patients with metastatic NSCLC that progressed on previous therapy. Given the improved disease-control rates of this combination compared with previous data obtained with erlotinib alone, everolimus 5 mg per day combined with erlotinib 150 mg per day was compared with erlotinib 150 mg per day alone in a randomized phase II study of second- or third-line therapy for patients with NSCLC. This trial is complete, and data analysis is underway.

ACKNOWLEDGMENTS

The authors thank Roland Tacke, PhD, and Matthew Hasson, BA, of Scientific Connexions for providing assistance with medical writing and copy editing.

This study was supported by Novartis Pharmaceuticals Corporation.

REFERENCES

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010;127:2893–2917.
2. National Comprehensive Cancer Network, Inc. NCCN Clinical Practice Guidelines in Oncology®: Non-Small Cell Lung Cancer. 2012. (Version 2.2012.) Available at: http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed March 18, 2012.
3. National Cancer Institute. SEER Cancer Statistics Review 1975–2008. Table 15.14: Non–small cell cancer of the lung and bronchus (invasive), 5-year relative and period survival (percent) by race, sex, diagnosis year, stage, and age. Available at: http://seer.cancer.gov/csr/1975_2008/browse_csr.php?section=15&page=sect_15_table.14.html. Accessed
4. D'Addario G, Früh M, Reck M, Baumann P, Klepetko W, Felip E; ESMO Guidelines Working Group. Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010;21(Suppl 5):v116–v119.
5. Crinò L, Weder W, van Meerbeeck J, Felip E; ESMO Guidelines Working Group. Early stage and locally advanced (non-metastatic) non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010;21(Suppl 5):v103–v115.
6. Kwak EL, Bang YJ, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *N Engl J Med* 2010;363:1693–1703.
7. Azzoli CG, Temin S, Aliff T, et al.; American Society of Clinical Oncology. 2011 Focused Update of 2009 American Society of Clinical Oncology Clinical Practice Guideline Update on Chemotherapy for Stage IV Non-Small-Cell Lung Cancer. *J Clin Oncol* 2011;29:3825–3831.
8. Rocha-Lima CM Raez LE. Erlotinib (tarceva) for the treatment of non-small-cell lung cancer and pancreatic cancer. *P T* 2009;34:554–564.
9. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al.; National Cancer Institute of Canada Clinical Trials Group. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 2005;353:123–132.
10. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009;361:947–957.
11. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med* 2004;350:2129–2139.
12. Paez JG, Jänne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science* 2004;304:1497–1500.
13. Faivre S, Kroemer G, Raymond E. Current development of mTOR inhibitors as anticancer agents. *Nat Rev Drug Discov* 2006;5:671–688.
14. Afinitor® (everolimus) tablets for oral administration [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2011.
15. Brognard J, Clark AS, Ni Y, Dennis PA. Akt/protein kinase B is constitutively active in non-small cell lung cancer cells and promotes cellular survival and resistance to chemotherapy and radiation. *Cancer Res* 2001;61:3986–3997.
16. Balsara BR, Pei J, Mitsuuchi Y, et al. Frequent activation of AKT in non-small cell lung carcinomas and preneoplastic bronchial lesions. *Carcinogenesis* 2004;25:2053–2059.
17. Bianco R, Troiani T, Tortora G, Ciardiello F. Intrinsic and acquired resistance to EGFR inhibitors in human cancer therapy. *Endocr Relat Cancer* 2005;12(Suppl 1):S159–S171.
18. Soria JC, Shepherd FA, Douillard JY, et al. Efficacy of everolimus (RAD001) in patients with advanced NSCLC previously treated with chemotherapy alone or with chemotherapy and EGFR inhibitors. *Ann Oncol* 2009;20:1674–1681.
19. Buck E, Eyzaguirre A, Brown E, et al. Rapamycin synergizes with the epidermal growth factor receptor inhibitor erlotinib in non-small-cell lung, pancreatic, colon, and breast tumors. *Mol Cancer Ther* 2006;5:2676–2684.
20. Johnson BE, Jackman D, Jänne PA. Rationale for a phase I trial of erlotinib and the mammalian target of rapamycin inhibitor everolimus (RAD001) for patients with relapsed non small cell lung cancer. *Clin Cancer Res* 2007;13(15 Pt 2):s4628–s4631.
21. O'Donnell A, Faivre S, Burris HA 3rd, et al. Phase I pharmacokinetic and pharmacodynamic study of the oral mammalian target of rapamycin inhibitor everolimus in patients with advanced solid tumors. *J Clin Oncol* 2008;26:1588–1595.
22. Tabernero J, Rojo F, Calvo E, et al. Dose- and schedule-dependent inhibition of the mammalian target of rapamycin pathway with everolimus: a phase I tumor pharmacodynamic study in patients with advanced solid tumors. *J Clin Oncol* 2008;26:1603–1610.
23. Tanaka C, O'Reilly T, Kovarik JM, et al. Identifying optimal biologic doses of everolimus (RAD001) in patients with cancer based on the modeling of preclinical and clinical pharmacokinetic and pharmacodynamic data. *J Clin Oncol* 2008;26:1596–1602.
24. National Cancer Institute. Common Terminology Criteria for Adverse Events v3.0 (CTCAE). National Cancer Institute Web site. Available at: http://ctep.cancer.gov/reporting/ctc_v30.html. Accessed July 13, 2011.
25. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;92:205–216.
26. Motzer RJ, Escudier B, Oudard S, et al.; RECORD-1 Study Group. Phase 3 trial of everolimus for metastatic renal cell carcinoma: final results and analysis of prognostic factors. *Cancer* 2010;116:4256–4265.
27. Yao JC, Shah MH, Ito T, et al.; RAD001 in Advanced Neuroendocrine Tumors, Third Trial (RADIANT-3) Study Group. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med* 2011;364:514–523.
28. Perez-Soler R. Phase II clinical trial data with the epidermal growth factor receptor tyrosine kinase inhibitor erlotinib (OSI-774) in non-small-cell lung cancer. *Clin Lung Cancer* 2004;6(Suppl 1):S20–S23.
29. Milton DT, Riely GJ, Azzoli CG, et al. Phase 1 trial of everolimus and gefitinib in patients with advanced nonsmall-cell lung cancer. *Cancer* 2007;110:599–605.
30. Price KA, Azzoli CG, Krug LM, et al. Phase II trial of gefitinib and everolimus in advanced non-small cell lung cancer. *J Thorac Oncol* 2010;5:1623–1629.
31. Stinchcombe TE Socinski MA. Current treatments for advanced stage non-small cell lung cancer. *Proc Am Thorac Soc* 2009;6:233–241.

