Feasibility of Adding Everolimus to Carboplatin and Paclitaxel, With or Without Bevacizumab, for Treatment-Naive, Advanced Non–Small Cell Lung Cancer

Wilfried E.E. Eberhardt, MD;^{*} Paul Mitchell, MD;[†] Joan H. Schiller, MD;[‡] Michael P. Brown, MBBS, PhD;[§] Michael Thomas, MD;^{||} Glenn Mills, MD;[¶] Valentine Jehl, MSc;[#] Shweta R. Urva, PhD;^{**} Jeffrey J. De Leo, BS;^{**} Sven Gogov, MD;[#] Vassiliki Papadimitrakopoulou, MD^{‡‡}

^{*}Department of Medical [Oncology](#)~~ine (Cancer Res.)~~, Universitätsklinikum Essen, West German Cancer Centre, Essen, Germany; [†]Ludwig Oncology Unit, Austin Hospital, Melbourne, Australia; [‡]University of Texas Southwestern Medical Center, Dallas, TX, USA; [§]Cancer Clinical Trials Unit, Royal Adelaide Hospital, Adelaide, Australia; ^{||}[Internistische Onkologi der Thoraxtumoren, e/Innere Med., Thoraxklinik im Universitätsklinikum, Heidelberg, Translational Lung Research Center Heidelberg \(TLRC-H\), German Center for Lung Research, Heidelberg, Germany](#); [¶]Louisiana State University Health Sciences Center/Feist-Weiller Cancer Center, Shreveport, LA, USA; ^{**}Novartis Pharmaceuticals Corporation, Florham Park, NJ, USA; [#]Novartis Pharmaceuticals Corporation, Basel, Switzerland; ^{‡‡}The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Corresponding author:

Wilfried Ernst Erich Eberhardt, MD

Department of [Medical Oncology](#)~~Medicine (Cancer Research)~~
West German Cancer Centre

University Hospital Essen

University Duisburg-Essen

Hufelandstrasse 55

45122 Essen, Germany

E-mail: wilfried.eberhardt@uni-essen.de

Phone: +49 201 723 3312 or +49 201 433 4559

Fax: +49 201 723 3114

Abstract

Introduction: One standard of care for advanced non–small cell lung cancer (NSCLC) is paclitaxel plus carboplatin±bevacizumab. This two-step phase I study evaluated the feasibility of adding everolimus to paclitaxel plus carboplatin±bevacizumab for advanced NSCLC.

Methods: Adults with advanced NSCLC naive to systemic therapy were enrolled. A Bayesian dose-escalation model was used to identify feasible daily or weekly everolimus doses given with paclitaxel (200 mg/m² q21 days) and carboplatin (200 mg/m² day 1; AUC 6 mg/mL/min day 1; qd 2221 days) (= (step 1) and paclitaxel (200 mg/m² q21 days), carboplatin (AUC 6 mg/mL/min q21 days), and bevacizumab (200 mg/m² 15 mg/kg day 1; AUC 6 day 1; 15 mg/kg day 1; qd 2221 days) (= (step 2). Primary endpoint was end-of-cycle 1 dose-limiting toxicity (DLT) rate. Secondary endpoints included safety; relative dose intensities of paclitaxel, carboplatin, and bevacizumab; pharmacokinetics; and tumor response.

Results: Fifty-two patients were enrolled and received everolimus 5 mg/day plus carboplatin and paclitaxel (step 1 daily; n=13); everolimus 30 mg/week plus carboplatin and paclitaxel (step 1 weekly; n=13); everolimus 5 mg/day plus carboplatin, paclitaxel, and bevacizumab (step 2 daily; n=13); or everolimus 30 mg/week plus carboplatin, paclitaxel, and bevacizumab (step 2 weekly; n=13). End-of-cycle 1 DLT rate was 16.7% (step 1 daily), 30.8% (step 1 weekly), 30.0% (step 2 daily), and 16.7% (step 2 weekly). Cycle 1 DLTs were grade 3 neutropenia, anal abscess, diarrhea, and thrombocytopenia and grade 4 myalgia, cellulitis, neutropenia, febrile neutropenia, pulmonary embolism, and thrombocytopenia. The most common adverse events were neutropenia, fatigue, anemia, and thrombocytopenia. One patient (step 2 daily) experienced complete response; 10 patients experienced partial response.

Conclusions: The feasible everolimus doses given with carboplatin and paclitaxel±bevacizumab were 5 mg/day and 30 mg/week. Neither schedule was very well tolerated in this unselected NSCLC population.

Key words: non–small cell lung cancer; everolimus; dose-limiting toxicity

Introduction

In patients with ~~advanced~~ (stage IIIB/IV) non-small cell lung cancer (NSCLC), platinum-based chemotherapy prolongs survival and improves symptom control when ~~used in combination~~ given with third-generation cytotoxic agents [1]. Accumulating evidence suggests that even newer platinum-based combinations including ~~that include~~ gemcitabine, vinorelbine, paclitaxel, and docetaxel, as well as pemetrexed for non-squamous cell carcinoma, have reached a plateau in their attainable overall response and efficacy, with 1-year survival rates of approximately 30%–40% [1–3]. Thus, despite recent advances in chemotherapy, including new strategies to deliver prolonged cytostatics ~~administration of cytostatics~~ via switch or continuation ~~maintenance and continuation~~ maintenance treatment with pemetrexed in select patients ~~populations~~, and the development of molecularly targeted agents, the prognosis for advanced NSCLC ~~overall~~ continues to be poor, with a median ~~overall~~ survival of ≤ ~~approximately~~ 12 months ~~or less~~ in unselected patients [2, 3]. ~~Novel therapeutic agents are urgently needed to further improve outcomes in advanced NSCLC.~~

Based on current knowledge of cellular pathways in lung cancer, several new ~~molecularly targeted therapies~~ targets are being pursued. One ~~target~~ is the mammalian target of rapamycin (mTOR), a signal transduction molecule implicated in cancer ~~the~~ development and progression ~~of cancer~~ [4]. Everolimus is an oral mTOR inhibitor that has shown antitumor activity in in vitro and in vivo tumor models [5–7], including NSCLC cell lines [5, 8–10]. Everolimus is currently approved in various countries for ~~treating~~ treating hormone receptor-positive, ~~her~~ HER ~~human epidermal growth factor receptor 2~~ –negative advanced breast cancer in combination with exemestane after failure of anastrozole or letrozole; sorafenib- or sunitinib-refractory advanced

renal cell carcinoma; progressive; unresectable, locally advanced or metastatic pancreatic neuroendocrine tumors ~~that are unresectable, locally advanced, or metastatic~~; subependymal giant cell astrocytomas not amenable to surgery in patients with tuberous sclerosis; and renal angiomyolipoma not requiring immediate surgery in patients with tuberous sclerosis [11–14].

~~E~~~~As monotherapy,~~ everolimus monotherapy has demonstrated modest clinical activity in ~~previously~~ treated advanced NSCLC [15]. However, preclinical data suggest ~~that~~ adding everolimus to cytotoxic ~~s~~agents may provide improved activity [5, 16]. In one study, everolimus sensitized ~~A549~~ human NSCLC cells to cisplatin-induced apoptosis, thereby demonstrating the potential to enhance the cisplatin therapeutic window [5]. In another study ~~of A549 cells,~~ everolimus demonstrated synergy with cisplatin and moderate synergy with paclitaxel [16]. ~~In vivo studies of H 596~~ NSCLC xenograft studies demonstrated dose-dependent synergy between everolimus and cisplatin and synergy between everolimus and low-dose paclitaxel [16]. Clinical evidence for ~~the~~ benefit of adding everolimus to cytotoxic chemotherapy in NSCLC comes from a phase I study of everolimus plus docetaxel for advanced NSCLC that progressed following ≥ 1 chemotherapy regimen [15].

Carboplatin plus paclitaxel ~~$\pm$ /-~~ ~~with or without~~ bevacizumab confers significant survival benefits in ~~for patients with~~ advanced NSCLC [17]. and ~~As such, this regimen~~ has become one of the standards of care for ~~treating~~ advanced NSCLC. Here, we report ~~the~~ results of a 2-step, phase I study designed to assess the feasibility of administering everolimus ~~in combination~~ with carboplatin and paclitaxel (step 1) or carboplatin, paclitaxel, and bevacizumab (step 2) in patients

with advanced, metastatic NSCLC not previously treated with systemic anticancer therapy (ClinicalTrials.gov unique identifier NCT00457119).

Methods

Patients

Eligible patients were aged ≥ 18 years with histologically or cytologically ~~proven~~confirmed advanced ~~NSCLC~~ (stage IIIB/IV ~~per Union Internationale Contre le Cancer of staging system [UICC/IASLC] 6 disease staging system~~) ~~NSCLC~~ [18] ~~not~~previously ~~untreated~~ with systemic therapy for advanced disease (~~no previous~~ systemic therapy for operable disease [eg, adjuvant chemotherapy or a combination of chemoradiotherapy chemotherapy and radiation]) ~~was~~ was permitted). Other key eligibility criteria included a World Health Organization (WHO) performance status ≤ 1 and adequate bone marrow, hepatic, and renal function. ~~Women of childbearing potential were required to demonstrate a negative serum pregnancy tests at screening.~~ Key exclusion criteria included severe and/or uncontrolled medical conditions, wide-field radiation therapy to $\geq 25\%$ of ~~the~~ bone marrow within 4 weeks of study ~~entry~~initiation, limited radiation therapy for palliation within 2 weeks before first study treatment, previous therapy with everolimus or other mTOR inhibitors, or known sensitivity to carboplatin (or other platinum-containing ~~derivatives~~agentscompounds), paclitaxel (or other taxanes), or bevacizumab. Patients with squamous cell histology, brain metastasis, history of thrombotic or hemorrhagic disorders, gross hemoptysis, or an international normalized ratio >1.5 and a partial thromboplastin time above the upper limit of normal within 1 week prior to study treatment were excluded from step 2.

Study design

This open-label, multicenter, two-step, phase I study was designed using a Bayesian sequential dose-escalation scheme based on a time-to-event model of the dose-limiting toxicity (DLT) rate, which estimates the probability that a patient will experience a DLT within their first treatment cycle (ie, end-of-cycle 1 DLT rate). Adverse events (AEs) meeting the definition of a DLT are summarized in Table 1. A time-to-event model was selected to ensure ~~a prompt reaction~~ response to the occurrence of any DLT during the first treatment cycle. The model used all DLTs occurring within a given regimen irrespective of when they occurred ~~during the treatment period, including during the first treatment cycle~~ 1. This design allowed flexibility ~~regarding~~ with regard ~~to~~ the number of patients enrolled at each dose level, avoiding the need ~~to for~~ predefined the cohort sizes s.

The ~~DLT~~ model was regularly updated to allow decision making about the next dose level to consider ~~for additional patients~~. Decision-making time points occurred after every DLT occurring within ~~the first treatment~~ cycle 1, after the first 6 patients in a schedule completed cycle 1 or had documented discontinuation due to a DLT during cycle 1, and, in the absence of the first two criteria, every 2 months thereafter. At each time point, the next dose level chosen was that which maximized the probability of the end-of-cycle 1 DLT rate falling within the targeted toxicity interval [20%–35%), had a <5% probability of the end-of-cycle 1 DLT rate falling within unacceptable toxicity interval [60%–100%] and a <25% probability of it falling within the excessive [35%–60%) or unacceptable [60%–100%] toxicity intervals combined.

The study was conducted according to the [Declaration of Helsinki](#) ethical principles ~~of the Declaration of Helsinki~~. The study protocol was reviewed by ~~the~~ independent ethics committees or institutional review boards for each participating center. Written informed consent was obtained from each patient before study enrollment.

Study treatment

The study was conducted in two successive steps. In step 1, patients received intravenous paclitaxel (200 mg/m² over 3 hours) followed 60 minutes later by intravenous carboplatin (area under the curve of 6 mg/mL/min over 30 minutes) on day 1 of a 21-day cycle. In step 2, intravenous bevacizumab (15 mg/kg over 90 minutes) was given 60 minutes after carboplatin.

During both steps, everolimus was administered orally on ~~a~~ daily (days 1–21) or weekly (days 1, 8, and 15) schedules. In cycle 1, everolimus dosing began on day 2 to permit serial blood sampling for pharmacokinetic evaluation of carboplatin and paclitaxel in the absence of everolimus. The starting [everolimus](#) doses ~~of everolimus~~ were 5 mg/day and 30 mg/week.

Within each step and schedule, up to two additional dose levels were planned: 2.5 and 10 mg/day and 20 and 50 mg/week. Per clinical guidelines [19, 20], all patients received standard [supportive](#) antiemetic therapy ~~before study drug administration~~.

Patients in steps 1 and 2 who completed the core treatment phase (ie, the first 6 treatment cycles) or who discontinued chemotherapy early entered the extension phase. During this phase, maintenance treatment with everolimus (patients from step 1) or everolimus plus bevacizumab (patients from step 2) was continued until disease progression, unacceptable toxicity, or [consent](#) withdrawal ~~of consent~~.

Study objectives

The primary study objective was to establish the feasible [everolimus](#) doses/regimens ~~of everolimus~~ given with carboplatin and paclitaxel (step 1) or carboplatin, paclitaxel, and bevacizumab (step 2) based on an evaluation of safety during the core treatment phase.

Secondary objectives included ~~the determination of~~ [the relative dose intensities \(RDIs\) of carboplatin, paclitaxel, and bevacizumab](#) [relative dose intensities \(RDIs\)](#); ~~assessment of~~ [the influence of carboplatin and paclitaxel on](#) [the everolimus pharmacokinetics of everolimus](#); and ~~determination of~~ [the best overall tumor response according to the Response Evaluation Criteria in Solid Tumors \(RECIST\), version 1.0 \[21\].](#)

Safety assessments included continuous AE collection; ~~weekly~~ [regular monitoring of](#) hematology [monitoring](#); and [physical examination and assessment of vital signs, body weight, coagulation, blood chemistry, and urinalysis, and monitoring](#); and ~~regular assessments of~~ electrocardiograms ~~performed every 3 weeks~~ (step 2 only, ~~three weekly~~) [every 3 weeks, and weekly assessment of vital signs, physical condition, body weight, and WHO performance status assessment](#). AEs were assessed according to the Common Terminology Criteria for Adverse Events, version 3.0.

Blood samples for pharmacokinetic assessment of daily everolimus were collected predose and 0.5, 1, 2, 4, and 24 hours postdose on day 8 of cycle 1 and day 1 of cycle 2; samples for ~~assessment of~~ weekly everolimus were collected predose and 0.5, 1, 2, 4, 24, and 168 hours postdose. Additional predose samples were collected during cycles 3 through 6. Blood samples for [carboplatin and paclitaxel pharmacokinetic](#) ~~assessment of carboplatin and paclitaxel~~

pharmacokinetics were collected 24 hours after paclitaxel ~~was administration~~ administered on day 1 of cycle 1 (~~when administered ie~~, without everolimus) and predose and 24 hours after paclitaxel ~~was administration~~ administered on day 1 of cycle 2 (~~in presence of ie~~, with everolimus). At each time point, 2 mL ~~of~~ venous blood was collected into a tube containing sodium heparin or EDTA. Everolimus ~~pharmacokinetic~~ samples were frozen at or below -20°C until shipment. Everolimus concentrations in whole blood were determined by a liquid chromatography–mass spectrometry method (~~with a~~ lower limit of quantification [~~(LLOQ)~~], ~~of~~ 0.3 ng/mL). Carboplatin and paclitaxel ~~Blood samples for carboplatin and paclitaxel assessment~~ were centrifuged at 3°C – 5°C for 10 minutes at $\sim 1500g$; plasma was transferred to polypropylene tubes and stored at or below -80°C until analysis. Carboplatin and paclitaxel concentrations were measured using validated liquid chromatography–tandem mass spectrometry methods (~~with~~ LLOQs ~~of~~ 0.1 $\mu\text{g/mL}$ and 1 ng/mL, respectively). Everolimus pharmacokinetic parameters of maximum concentration (C_{max}), time to reach C_{max} (t_{max}), trough concentration (C_{min}), ~~the~~ area under the curve from time 0 to last measurable concentration ($\text{AUC}_{0-\text{last}}$), and AUC in the dosing interval (AUC_{tau}) were derived by noncompartmental analysis using WinNonlin Version 5.2 (Pharsight, Mountain View, CA, USA).

Tumor measurements were assessed using chest and upper abdomen computed tomography (CT) scans ~~of the chest and upper abdomen~~ performed at baseline and repeated ~~at the end of~~ after cycles 2, 4, and 6 during the core phase and every 6–8 weeks during the extension ~~phase~~. Brain ~~Cranial~~ magnetic resonance imaging or CT was performed at baseline ~~for patients~~ in step 2 only. Complete or partial responses according to RECIST, ~~version 1.0~~, required confirmation

using the same assessment method ≥ 4 weeks after initial response observation ~~of response was initially observed.~~

Statistical analysis

No formal sample size calculation was performed. It was anticipated that approximately 30 patients would be sufficient to complete dose escalation within a given regimen and ensure ~~that~~ the desired confidence level ~~of confidence~~ in the end-of-cycle 1 DLT rate and carboplatin, paclitaxel, and bevacizumab (step 2 only) RDIs ~~for carboplatin, paclitaxel, and bevacizumab (step 2 only)~~ would be reached.

The full analysis set included all patients who received ≥ 1 dose of any study treatment. The safety population included all patients who received ≥ 1 dose of any ~~of the~~ study treatments and had ≥ 1 postbaseline safety assessment. The dose-determining population included all patients from the safety population who met the minimum exposure requirement (≤ 7 daily or ≤ 1 weekly everolimus dose missed and paclitaxel and bevacizumab RDIs of $\geq 95\%$ and carboplatin RDI ~~of~~ $\geq 80\%$ in cycle 1) or who experienced a DLT at any time during the core phase. The pharmacokinetic population included all patients in the safety population who had eligible trough samples and pharmacokinetic parameters. ~~The full analysis set included all patients who received ≥ 1 dose of any study treatment.~~

Results

Patients

Of ~~the~~ 70 patients screened, 52 were enrolled ~~onto~~in the study between March 2007 and March 2009, with 26 patients each allocated to steps 1 and 2; in each step, 13 ~~patients~~ received ~~the~~ daily ~~everolimus schedule~~ and 13 received ~~the~~ weekly ~~schedule~~ everolimus (Figure 1). Of ~~the~~ 52 patients enrolled, 15 completed the core treatment phase and 14 entered the extension phase. AEs were the most common reason for discontinuation during the core phase ($n=20$).

In the total study population, 61.5% of patients were aged <65 years, 48.1% were women, 86.5% had stage IV disease, 80.8% were current or former smokers, and 63.5% had a WHO performance status of 1 (Table 2). Within steps 1 and 2, baseline demographics were broadly comparable across ~~the~~ treatment schedules. ~~However, i~~Imbalances were noted between steps 1 and 2. In step 1, the majority of patients were men (57.7%), whereas women ~~made up~~were the majority in step 2 (53.8%). More patients in step 2 were aged <65 years (69.2% vs 53.8% in step 1). ~~Although the majority of patients in both steps were aged <65 years, the proportion of such patients was greater in step 2 than in step 1 (69.2% vs 53.8%).~~

Dose-limiting toxicities

In the dose-determining population ($n=47$), the percentage of patients who experienced a DLT during any cycle was 68.0% for step 1 and 81.8% for step 2 (Table 3). Cycle 1 DLTs were observed in 2 ~~patients~~ (16.7%) and 4 ~~patients~~ (30.8%) patients in the step 1 daily and weekly schedules ~~of step 1~~, respectively. In step 2, cycle 1 DLTs were observed in 3 ~~patients~~ (30.0%) ~~in the daily schedule~~ and 2 ~~patients~~ (16.7%) patients in the daily and ~~of patients in the~~ weekly

schedules s, respectively. Neutropenia was the most common DLT ~~observed~~, with the highest incidence in the step 2 daily schedule ~~of step 2~~. The other DLTs ~~observed throughout the study~~ were bacterial sepsis, dehydration, fatigue, febrile neutropenia, lower respiratory tract infection, peripheral neuropathy, thrombocytopenia, and urosepsis in the step 1 daily schedule ~~of step 1~~; cellulitis, febrile neutropenia, hypophosphatemia, myalgia, pulmonary embolism, pneumonia, pneumonitis, and thrombocytopenia in the step 1 weekly schedule ~~of step 1~~; anal abscess, colitis, diarrhea, febrile neutropenia, gastroenteritis, hypokalemia, and increased aspartate aminotransferase in the step 2 daily schedule ~~of step 2~~; and colitis, fatigue, peripheral neuropathy, pneumothorax, and thrombocytopenia in the step 2 weekly schedule ~~of step 2~~.

After four decision-making points in step 1, with 13 patients enrolled in each ~~of the daily and weekly~~ treatment schedules, everolimus 5 mg/day and 30 mg/week ~~was were~~ declared as the ~~to be the~~ feasible ~~daily doses and 30 mg/week as the feasible weekly schedule~~. Based on these outcomes, step 1 enrollment was considered complete and step 2 enrollment was ~~sequentially~~ initiated at everolimus 5 mg/day and 30 mg/week. After two decision-making points ~~in step 2~~, with 7 patients enrolled in each schedule, the Bayesian model suggested escalating ~~the~~ everolimus ~~doses~~ to 10 mg/day and 50 mg/week. However, ~~it was decided that~~ everolimus dosing was ~~would not be~~ increased due to toxicity concerns (increased DLTs in later cycles and hematologic toxicity), and recruitment continued at 5 mg/day and 30 mg/week until 13 patients were enrolled in each schedule. E~~The~~ end-of-cycle 1 DLT posterior probability rates based on the Bayesian model are summarized in Table 3.

Adverse events

All patients reported ≥ 1 AE (Table 4). Neutropenia was the most frequently reported AE and occurred at ~~a~~ similar rates in all treatment arms (84.6% in the daily schedules of steps 1 and 2 and 76.9% in the weekly schedules of steps 1 and 2). Additional AEs reported in $>50\%$ of patients in either ~~treatment~~ arm of step 1 were anemia, leukopenia, thrombocytopenia, fatigue, and alopecia and in step 2, fatigue, nausea, epistaxis, thrombocytopenia, anemia, and alopecia. Most patients (90.4%) also experienced ~~a~~ grade 3/4 AEs, most frequently neutropenia (73.1%) and leukopenia (42.3%) (Table 4). ~~I~~The incidence of grade 3/4 AEs was generally similar across treatment arms. Serious AEs were experienced by 55.8% ~~of patients~~ (Table 4). ~~Interestingly,~~ ~~n~~Noninfectious pneumonitis of grade ≥ 3 ~~or higher~~ was not identified as a major nonhematologic toxicity in any schedule or step ~~of the trial~~. No deaths were reported during study treatment or ~~within in the~~ 28 days thereafter.

Overall, more patients in step 2 experienced AEs leading to treatment discontinuation (53.8% vs 34.6% in step 1), with the highest incidence observed in the step 2 weekly schedule ~~of step 2~~ (69.2%) (Table 4). ~~Specific~~ AEs that led to treatment discontinuation in ≥ 2 patients were peripheral neuropathy ($n=5$) and neutropenia and thrombocytopenia ($n=2$ each).

Exposure and relative dose intensity

~~The duration of exposure to study treatment during the core treatment phase is summarized in Table 5.~~ In step 1, ~~the~~ median duration of exposure to combination therapy was 13.43 weeks in the daily schedule and 9.29 weeks in the weekly schedule (Table 5). In step 2, ~~the~~ median duration of exposure was similar (~~16.43 and 13.29~~ weeks in the daily ~~schedule and 13.29 weeks~~

~~in the~~ and weekly schedules, respectively). Among the ~~8~~ eight patients ~~entering~~ who entered the step 1 extension phase ~~of step 1 (ie, received everolimus alone)~~, the median duration of everolimus exposure was 7 weeks. In step 2, four patients entered the extension ~~phase~~ and received everolimus and bevacizumab; ~~and~~ an additional two patients received everolimus alone. Among these patients, ~~the~~ median duration of exposure was 18 weeks.

In step 1, the carboplatin and paclitaxel RDIs ~~for carboplatin and paclitaxel~~ were similar in the daily and weekly schedules (Table 5). In step 2, the carboplatin, paclitaxel, and bevacizumab RDIs ~~for carboplatin, paclitaxel, and bevacizumab~~ were higher in the weekly than the daily schedule (Table 5). Regardless of ~~the~~ step or schedule, the majority of patients had an RDI that fell within the 0.70 to <1.10 range (data not shown).

Pharmacokinetics

In the step 1 daily schedule ~~of step 1~~, ~~the parameter estimates for~~ everolimus AUC_{0-last} , AUC_{tau} , and C_{max} estimates suggested a trend towards a greater than dose-proportional increase when everolimus was administered with carboplatin and paclitaxel (Table 6). In the step 2 daily schedule ~~of step 2~~, ~~the estimates for~~ everolimus AUC_{0-last} and AUC_{tau} estimates suggested a less than dose-proportional increase when everolimus was administered with carboplatin, paclitaxel, and bevacizumab, whereas a greater than dose-proportional increase for C_{max} was suggested (Table 6). ~~However, f~~ For both steps ~~1 and 2~~, the 90% confidence intervals associated with beta were wide and crossed unity, suggesting a large variability in ~~the~~ model estimates. Similar results were obtained for steps 1 and 2 of the weekly everolimus schedule (data not shown).

Carboplatin plus paclitaxel did not influence the AUC_{0-last} , AUC_{tau} , or C_{max} of ~~the~~ daily or weekly everolimus ~~schedules of~~in step 1 (data not shown). In step 2, minor decreases in everolimus AUC_{0-last} , AUC_{tau} , and C_{max} were noted in the daily schedule when everolimus was given ~~in combination~~ with carboplatin, paclitaxel, and bevacizumab compared with being given alone; ~~however~~, in the weekly schedule, the carboplatin/paclitaxel/bevacizumab combination did not appear to influence these ~~pharmacokinetic~~ parameters (data not shown).

Efficacy

The most frequent best overall response across treatment arms was stable disease (Table 7). One patient in step 2 treated with the daily schedule achieved ~~a~~ complete response. Two patients in each daily schedule and three patients in each weekly schedule achieved ~~a~~ partial response. ~~Overall, o~~Objective response rates (percentage of patients with complete or partial response) were 15.4% for the step 1 daily schedule and 23.1% for the remaining 3 schedules. ~~D~~The disease control rate (percentage of patients with complete or partial response or stable disease) was 61.5% and 69.2% in the daily ~~schedules and 69.2% in~~and the weekly schedules, respectively. Median progression-free survival (~~PFS~~) ranged from 5.1 months (95% CI, 1.6–8.4 months) in the step 1 daily schedule ~~of step 1~~ to 9.0 months (95% CI, 2.7–10.2 months) in the step 2 weekly schedule ~~of step 2~~ (Table 7).

Discussion

Based on ~~the need to improve outcomes in advanced NSCLC and~~ preclinical and clinical evidence suggesting ~~the~~ benefits of ~~for~~ adding everolimus to cytotoxic chemotherapy, the present

~~study~~~~clinical trial~~ was conducted to identify feasible everolimus doses ~~of everolimus~~ given ~~combined within combination with~~ carboplatin plus paclitaxel $\pm$ +/- ~~with or without~~ bevacizumab in ~~patients with~~ previously untreated advanced and metastatic NSCLC. (At the time of this ~~trial study~~ ~~was designed~~, carboplatin plus paclitaxel $\pm$ +/- ~~with or without~~ bevacizumab was a standard ~~chemotherapy~~ regimen). Based on the probability of the end-of-cycle 1 DLT rate falling within the targeted toxicity interval ~~(ie, the primary study endpoint)~~, everolimus 5 mg/day and 30 mg/week were identified as the feasible ~~doses of~~ everolimus doses plus carboplatin and paclitaxel $\pm$ +/- ~~with or without bevacizumab in advanced NSCLC~~. However, given that 74% of patients experienced ≥ 1 DLT at any cycle, 44% ~~of patients~~ discontinued treatment due to AEs, and 56% ~~of patients~~ experienced ≥ 1 serious AE, this regimen may not be appropriate for long-term administration ~~use~~.

The model-derived end-of-cycle 1 DLT rate was similar across steps 1 and 2, whereas the DLT rate across all cycles was higher in step 2. ~~F~~~~At the end of the study, the final data~~ at study end showed that when given with ~~the combination of~~ carboplatin, paclitaxel, and bevacizumab, everolimus 5 mg/day (as opposed to 2.5 or 10 mg/day) maximized the chance of being within the targeted toxicity interval while reducing ~~maintaining the~~ risk of excessive and unacceptable toxicity (59% chance that end-of-cycle 1 DLT rate would be within the targeted toxicity interval and 14% chance ~~that~~ it would be within the excessive/unacceptable ~~toxicity~~ range). Based on these results, everolimus 5 mg/day was considered to be the feasible daily dose. Considering ~~the~~ weekly scheduling dosing, ~~the~~ final data showed that everolimus 30 mg/week ~~when given~~ combined in combination with carboplatin, paclitaxel, and bevacizumab was associated with a 29% chance ~~that~~ the end-of-cycle 1 DLT rate would be within the targeted toxicity interval and a

1% chance ~~that~~ it would be within the excessive/unacceptable toxicity interval. Although the final model showed that everolimus 50 mg/week provided the greatest chance ~~that~~ the end-of-cycle 1 DLT rate was within the targeted toxicity interval (44% vs 8% for 20 mg/week and 29% for 30 mg/week), the risk of excessive or unacceptable toxicity with 50 mg/week was considered unacceptable (27%). Therefore, everolimus 30 mg/week was considered ~~to be~~ the feasible weekly dose. The observed [carboplatin, paclitaxel, and bevacizumab](#) RDIs ~~for carboplatin, paclitaxel, and bevacizumab~~ suggest that everolimus 5 mg/day and 30 mg/week allow patients [in both the receiving both](#) daily and weekly ~~treatment~~ schedules to achieve adequate [drug](#) exposure ~~to these drugs~~. Given the small sample size, it is [not possible to conclude](#) ~~difficult to make meaningful conclusions regarding~~ which ~~of the two~~ schedules [should](#) ~~would~~ be preferred.

There were no unexpected safety signals observed when [adding](#) everolimus ~~was added to standard carboplatin and paclitaxel therapy +/- or carboplatin, paclitaxel, and bevacizumab therapy~~. All patients experienced ≥ 1 AE, and 90.4% experienced ≥ 1 grade 3/4 abnormality, most commonly neutropenia. The overall incidence of grade 3/4 abnormalities was comparable across steps 1 and 2. ~~Very few grade 3/4 biochemistry abnormalities were reported~~. Interestingly, the AE profile observed in this study was not generally consistent with the known everolimus safety profile. Many ~~of the~~ AEs frequently associated with everolimus, including noninfectious pneumonitis, hypersensitivity, hyperglycemia, and increased creatinine, were reported in [frequently](#) ~~very few patients~~, and while stomatitis, hypophosphatemia, lymphopenia, and dyslipidemic events were reported ~~among the study population~~, they were ~~reported only occasionally~~ [also infrequent](#) and ~~were~~ mostly of grade 1 ~~or~~ 2 severity. No wound-healing complications were noted. Overall, the AEs observed ~~in this study~~ were broadly consistent with

the Eastern Cooperative Oncology Group 4599 study of carboplatin plus paclitaxel ~~±/± with or without bevacizumab as first-line treatment of advanced NSCLC~~ [17], albeit with ~~an~~ increased d in the frequency and severity of reported AEs. This may be related ~~observation is likely due~~ to the overlapping toxicity profiles of carboplatin, paclitaxel, bevacizumab, and everolimus, ~~and which~~ may limit the ability to combine ~~of these drugs to be given in combined combination~~.

A dose-escalation study of everolimus monotherapy ~~performed~~ in patients with advanced solid tumors indicated ~~that~~ everolimus 10 mg/day and 50 mg/week resulted in maximum ~~in~~ inhibition of two downstream effectors of mTOR signaling, ribosomal protein S6 kinase 1 (S6K1) and eukaryotic initiation factor 4G (eIF-4G) [22]. ~~E~~In this study, everolimus 5 mg/day demonstrated near complete inhibition of S6K1 phosphorylation (pS6) and partial inhibition of eIF-4G phosphorylation (peIF-4G), whereas pS6 and peIF-4G were almost completely blocked with everolimus 10 mg/day [22]. ~~A s~~Similar inhibition profile was ~~also~~ seen with weekly dosing, where pS6 inhibition was almost complete at 20 mg/week, but sustained peIF-4G inhibition ~~of peIF-4G~~ was only apparent at doses ≥ 50 mg/week [22]. Thus, escalation beyond everolimus 10 mg/day and 50 mg/week may only risk ~~emergence of~~ additional toxicities without any further ~~effective inhibition of the~~ mTOR pathway inhibition. Subsequent dose-finding studies of everolimus monotherapy ~~conducted in patients with~~ for advanced solid tumors [23–25] have shown everolimus 5–10 mg/day or 20–50 mg/week to be well tolerated with modest clinical activity. In the present study of everolimus in combination with carboplatin and paclitaxel ~~±/± with or without bevacizumab in patients with~~ advanced, metastatic NSCLC, it is notable that the feasible everolimus monotherapy dose (10 mg/day) ~~dose previously identified as feasible for~~ monotherapy studies [23–25] was not evaluated due to toxicity concerns ~~and that everolimus 5~~

~~mg/day was declared to be the feasible dose.~~ Similarly, although everolimus 50 mg/week was identified as the feasible ~~ee-dose for everolimus~~ dose [22], 30 mg/week was identified as the feasible dose in ~~the-this present~~ study due to ~~the~~ cumulative toxicity conferred by carboplatin and paclitaxel ~~+/-with or without~~ bevacizumab. The identification of lower everolimus doses ~~of everolimus~~ when ~~combining it given with~~ used in combination with other anticancer agents is consistent with ~~findings of~~ findings from ~~of other studies of~~ combination ~~therapy~~ studies in NSCLC [15, 26, 27] and other solid tumors [28, 29].

~~P~~The pharmacokinetic evaluations ~~performed in our~~ this study showed a trend indicating a greater than dose-proportional increase in everolimus exposure when ~~everolimus is co-~~ administered ~~it ded~~ with ~~the~~ carboplatin and paclitaxel and a less than dose-proportional increase when ~~everolimus is~~ administered ~~it in combination~~ with carboplatin, paclitaxel, and bevacizumab. ~~Ultimately,~~ however, the wide confidence intervals associated with the observed ~~estimates of~~ dose proportionality estimates allow no final conclusions preclude firm conclusions ~~precluded the analysis from being conclusive.~~ ~~Concomitant administration of everolimus with both regimens~~ carboplatin and paclitaxel or carboplatin, paclitaxel, and bevacizumab did not appear to noticeably influence everolimus pharmacokinetics.

~~D~~Although it is difficult to draw any efficacy conclusions from this study due to the small sample size in this study, no valid efficacy conclusions can be drawn for efficacy of related to adding everolimus 5 mg/day and 30 mg/week ~~appeared to show modest efficacy when added to standard~~ carboplatin and paclitaxel ~~+/-with or without~~ bevacizumab can be drawn. ~~At t~~These doses and ~~,the treatment~~ schedules resulted in a disease control rate of 61.5%–69.2% and a

median ~~PFS~~ progression-free survival of 5.1–9.0 months in this molecularly unselected ~~patient~~ population. ~~M~~A more robust evaluation ~~of efficacy in a~~ specifically selected or and, ideally, molecularly ~~well~~-defined ~~patient~~ populations would be necessary to investigate ~~establish~~ whether everolimus could ~~improves~~ the therapeutic index of ~~standard therapy with~~ carboplatin and paclitaxel ±/± ~~with or without~~ bevacizumab in these subsets.

In conclusion, ~~b~~In conclusion and as based on the primary study endpoint of ~~the~~ end-of-cycle 1 DLT rate, the feasible everolimus doses ~~of everolimus when~~ given with carboplatin and paclitaxel ±/± ~~with or without~~ bevacizumab were 5 mg/day and 30 mg/week. These doses were not very well tolerated due to overlapping toxicities, with cytopenias, including neutropenia, the most common AEs ~~clinically notable ones~~ AEs observed. ~~Both the daily and weekly everolimus doses permitted adequate RDIs of carboplatin, paclitaxel, and bevacizumab, and the administration of carboplatin and paclitaxel ±/± with or without bevacizumab had no impact on the pharmacokinetics of everolimus. At the identified feasible doses of everolimus, both the daily and weekly schedules appeared to show modest efficacy.~~ B ~~Although efficacy was modest in this unselected NSCLC population, based on the known efficacy of everolimus monotherapy in pancreatic neuroendocrine tumors [30], a prospective phase II evaluation study of everolimus in combination with~~ plus carboplatin and paclitaxel as first-line therapy for stage IV large cell lung carcinoma ~~near~~ with neuroendocrine differentiation is currently ongoing ~~recruiting patients~~ (ClinicalTrials.gov identifier NCT01317615).

Acknowledgments

This study was supported by Novartis Pharmaceuticals Corporation. Editorial assistance in the preparation of this manuscript was provided by Melanie Leiby, PhD, of ApotheCom (Yardley, PA, USA) and was funded by Novartis Pharmaceuticals Corporation.

Conflict of Interest

Jeffrey De Leo, Sven Gogov, Valentine Jehl, and Shweta Urva are employees of Novartis Pharmaceuticals. Sven Gogov and Shweta Urva hold stock in Novartis Pharmaceuticals.

Wilfried Eberhardt has received support for travel to meetings for the study or other purpose and provision of writing assistance, medicines, equipment, or administrative support from Novartis Pharmaceuticals; served as a consultant for Novartis Pharmaceuticals; received payment for lectures including service on speakers bureaus from Novartis Pharmaceuticals; and payment for development of educational presentations from Novartis Pharmaceuticals.

Joan Schiller has received consulting fees or honorarium from Novartis Pharmaceuticals.

Michael P. Brown has received grant funding from Novartis and served as an advisory board member for Novartis.

Michael Thomas has received grants, consulting fees or honorarium, support for travel to meetings, and fees for participation in other review activities from Novartis Pharmaceuticals.

Glenn Mills and Vassiliki Papadimitrakopoulou have grant funding from Novartis Pharmaceuticals.

Paul Mitchell declares no conflict of interest.

References

1. National Comprehensive Cancer Network (2011) Nccn Clinical Practice Guidelines In Oncology: Non-Small Cell Lung Cancer, Version 2.2012
2. Ramalingam S, Sandler Ab (2006) Salvage Therapy For Advanced Non-Small Cell Lung Cancer: Factors Influencing Treatment Selection. *Oncologist* 11:655–665
3. Behera M, Owonikoko Tk, Chen Z, Kono Sa, Khuri Fr, Belani Cp, Ramalingam Ss (2012) Single Agent Maintenance Therapy For Advanced Stage Non-Small Cell Lung Cancer: A Meta-Analysis. *Lung Cancer* 77:331–338
4. Bjornsti Ma, Houghton Pj (2004) The Tor Pathway: A Target For Cancer Therapy. *Nat Rev Cancer* 4:335–348
5. Beuvink I, Boulay A, Fumagalli S, Zilbermann F, Ruetz S, O'reilly T, Natt F, Hall J, Lane Ha, Thomas G (2005) The Mtor Inhibitor Rad001 Sensitizes Tumor Cells To Dna-Damaged Induced Apoptosis Through Inhibition Of P21 Translation. *Cell* 120:747–759
6. Boulay A, Zumstein-Mecker S, Stephan C, Beuvink I, Zilbermann F, Haller R, Tobler S, Heusser C, O'reilly T, Stolz B, Marti A, Thomas G, Lane Ha (2004) Antitumor Efficacy Of Intermittent Treatment Schedules With The Rapamycin Derivative Rad001 Correlates With Prolonged Inactivation Of Ribosomal Protein S6 Kinase 1 In Peripheral Blood Mononuclear Cells. *Cancer Res* 64:252–261
7. Mabuchi S, Altomare Da, Connolly Dc, Klein-Szanto A, Litwin S, Hoelzle Mk, Hensley Hh, Hamilton Tc, Testa Jr (2007) Rad001 (Everolimus) Delays Tumor Onset And Progression In A Transgenic Mouse Model Of Ovarian Cancer. *Cancer Res* 67:2408–2413

8. La Monica S., Galetti M, Alfieri Rr, Cavazzoni A, Ardizzoni A, Tiseo M, Capelletti M, Goldoni M, Tagliaferri S, Mutti A, Fumarola C, Bonelli M, Generali D, Petronini Pg (2009) Everolimus Restores Gefitinib Sensitivity In Resistant Non-Small Cell Lung Cancer Cell Lines. *Biochem Pharmacol* 78:460–468

9. Nakachi I, Naoki K, Soejima K, Kawada I, Watanabe H, Yasuda H, Nakayama S, Yoda S, Satomi R, Ikemura S, Terai H, Sato T, Ishizaka A (2010) The Combination Of Multiple Receptor Tyrosine Kinase Inhibitor And Mammalian Target Of Rapamycin Inhibitor Overcomes Erlotinib Resistance In Lung Cancer Cell Lines Through C-Met Inhibition. *Mol Cancer Res* 8:1142–1151

10. Xu Cx, Li Y, Yue P, Owonikoko Tk, Ramalingam Ss, Khuri Fr, Sun Sy (2011) The Combination Of Rad001 And Nvp-Bez235 Exerts Synergistic Anticancer Activity Against Non-Small Cell Lung Cancer In Vitro And In Vivo. *Plos One* 6:E20899

11. Afinitor (Everolimus) Tablets For Oral Administration [Prescribing Information] (2012) East Hanover, Nj, Usa: Novartis Pharmaceuticals Corporation

12. Afinitor Summary Of Product Characteristics (2012) West Sussex, United Kingdom: Novartis Europharm Limited

13. Votubia Summary Of Product Characteristics (2012) West Sussex, United Kingdom: Novartis Europharm Limited

14. Baselga J, Campone M, Piccart M, Burris Ha, Rugo Hs, Sahmoud T, Noguchi S, Gnant M, Pritchard Ki, Lebrun F, Beck Jt, Ito Y, Yardley D, Deleu I, Perez A, Bachelot T, Vittori L, Xu Z, Mukhopadhyay P, Lebwohl D, Hortobagyi Gn (2012) Everolimus In

Postmenopausal Hormone Receptor-Positive Advanced Breast Cancer. *N Engl J Med* 366:520–529

15. Ramalingam Ss, Harvey Rd, Saba N, Owonikoko Tk, Kauh J, Shin Dm, Sun Sy, Strychor S, Tighiouart M, Egorin Mj, Fu H, Khuri Fr (2010) Phase 1 And Pharmacokinetic Study Of Everolimus, A Mammalian Target Of Rapamycin Inhibitor, In Combination With Docetaxel For Recurrent/Refractory Nonsmall Cell Lung Cancer. *Cancer* 116:3903–3909
16. O'reilly T, Mcsheehy Pm, Wartmann M, Lassota P, Brandt R, Lane Ha (2011) Evaluation Of The Mtor Inhibitor, Everolimus, In Combination With Cytotoxic Antitumor Agents Using Human Tumor Models In Vitro And In Vivo. *Anticancer Drugs* 22:58–78
17. Sandler A, Gray R, Perry Mc, Brahmer J, Schiller Jh, Dowlati A, Lilenbaum R, Johnson Dh (2006) Paclitaxel-Carboplatin Alone Or With Bevacizumab For Non-Small-Cell Lung Cancer. *N Engl J Med* 355:2542–2550
18. Goldstraw P, Crowley J, Chansky K, Giroux Dj, Groome Pa, Rami-Porta R, Postmus Pe, Rusch V, Sobin L (2007) The Iaslc Lung Cancer Staging Project: Proposals For The Revision Of The Tnm Stage Groupings In The Forthcoming (Seventh) Edition Of The Tnm Classification Of Malignant Tumours. *J Thorac Oncol* 2:706–714
19. Kris Mg, Hesketh Pj, Somerfield Mr, Feyer P, Clark-Snow R, Koeller Jm, Morrow Gr, Chinnery Lw, Chesney Mj, Gralla Rj, Grunberg Sm (2006) American Society Of Clinical Oncology Guideline For Antiemetics In Oncology: Update 2006. *J Clin Oncol* 24:2932–2947

20. Herrstedt J, Aapro Ms, Roila F, Kataja Vv (2005) Esmo Minimum Clinical Recommendations For Prophylaxis Of Chemotherapy-Induced Nausea And Vomiting (Nv). Ann Oncol 16 Suppl 1:I77–I79
21. Therasse P, Arbuck Sg, Eisenhauer Ea, Wanders J, Kaplan Rs, Rubinstein L, Verweij J, Van Glabbeke M, Van Oosterom At, Christian Mc, Gwyther Sg (2000) New Guidelines To Evaluate The Response To Treatment In Solid Tumors. J Natl Cancer Inst 92:205–216
22. Tabernero J, Rojo F, Calvo E, Burris H, Judson I, Hazell K, Martinelli E, Cajal S, Jones S, Vidal L, Shand N, Macarulla T, Ramos Fj, Dimitrijevic S, Zoellner U, Tang P, Stumm M, Lane Ha, Lebwohl D, Baselga J (2008) 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 26:1603–1610
23. O'donnell A, Faivre S, Burris Ha, Iii, Rea D, Papadimitrakopoulou V, Shand N, Lane Ha, Hazell K, Zoellner U, Kovarik Jm, Brock C, Jones S, Raymond E, Judson I (2008) Phase I Pharmacokinetic And Pharmacodynamic Study Of The Oral Mammalian Target Of Rapamycin Inhibitor Everolimus In Patients With Advanced Solid Tumors. J Clin Oncol 26:1588–1595
24. Xu B, Wu Y, Shen L, Ye D, Jappe A, Cherfi A, Wang H, Yuan R (2011) Two Dose-Level Confirmatory Study Of The Pharmacokinetics And Tolerability Of Everolimus In Chinese Patients With Advanced Solid Tumors. J Hematol Oncol 4:3

25. Okamoto I, Doi T, Ohtsu A, Miyazaki M, Tsuya A, Kurei K, Kobayashi K, Nakagawa K (2010) Phase I Clinical And Pharmacokinetic Study Of Rad001 (Everolimus) Administered Daily To Japanese Patients With Advanced Solid Tumors. *Jpn J Clin Oncol* 40:17–23
26. Milton Dt, Riely Gj, Azzoli Cg, Gomez Je, Heelan Rt, Kris Mg, Krug Lm, Pao W, Pizzo B, Rizvi Na, Miller Va (2007) Phase 1 Trial Of Everolimus And Gefitinib In Patients With Advanced Nonsmall-Cell Lung Cancer. *Cancer* 110:599–605
27. Vansteenkiste J, Solomon B, Boyer M, Wolf J, Miller N, Di Sl, Pylvaenaeinen I, Petrovic K, Dimitrijevic S, Anrys B, Laack E (2011) Everolimus In Combination With Pemetrexed In Patients With Advanced Non-Small Cell Lung Cancer Previously Treated With Chemotherapy: A Phase I Study Using A Novel, Adaptive Bayesian Dose-Escalation Model. *J Thorac Oncol* 6:2120–2129
28. Harzstark Al, Small Ej, Weinberg Vk, Sun J, Ryan Cj, Lin Am, Fong L, Brocks Dr, Rosenberg Je (2011) A Phase 1 Study Of Everolimus And Sorafenib For Metastatic Clear Cell Renal Cell Carcinoma. *Cancer* 117:4194–4200
29. Bullock Ke, Petros Wp, Younis I, Uronis He, Morse Ma, Blobe Gc, Zafar Sy, Gockerman Jp, Lager Jj, Truax R, Meadows Kl, Howard La, O'neill Mm, Broadwater G, Hurwitz Hi, Bendell Jc (2011) A Phase I Study Of Bevacizumab (B) In Combination With Everolimus (E) And Erlotinib (E) In Advanced Cancer (Bee). *Cancer Chemother Pharmacol* 67:465–474
30. Yao Jc, Shah Mh, Ito T, Bohas Cl, Wolin Em, Van Cutsem E, Hobday Tj, Okusaka T, Capdevila J, De Vries Eg, Tomassetti P, Pavel Me, Hoosen S, Haas T, Lincy J, Lebwohl D,

Oberg K (2011) Everolimus For Advanced Pancreatic Neuroendocrine Tumors. N Engl J Med 364:514–523

Figure Legend

Figure 1. Patient disposition. ^a13 of 14 patients who entered the extension phase discontinued it due to disease progression. One patient discontinued due to elevated carcinoembryonic antigen.

^b1 patient entered the extension phase having previously discontinued the core stage due to an AE. AE, adverse event; CP, carboplatin and paclitaxel; CPB, carboplatin, paclitaxel, and bevacizumab; DP, disease progression.

Table 1. Summary of Adverse Events that Met the Definition of a Dose-Limiting Toxicity

Adverse Event	Criteria
Febrile neutropenia (defined as ANC < 1 x 10 ⁹ /L and fever ≥38.5°C)	Of any duration
Grade 4 thrombocytopenia	Of any duration
Grade 3 or 4 neutropenia (non-febrile)	Taking >7 days to resolve to grade ≤1 or recurring within the same cycle
Grade 3 thrombocytopenia	Taking >7 days to resolve to grade ≤1 or recurring within the same cycle
Any grade 4 nonhematologic event (except hyperlipidemia and hyperglycemia) despite appropriate prophylactic treatment	Of any duration
Any grade 3 nonhematologic event (except hyperlipidemia, hyperglycemia, and pneumonitis), grade 2 pneumonitis, or other intolerable grade 2 event despite appropriate prophylactic treatment	Taking >7 days to resolve to grade ≤1 or recurring within the same cycle
Grade 3 pneumonitis	Of any duration

ANC, absolute neutrophil count.

Table 2. Patient Demographics, Baseline Characteristics and Disease History (Full Analysis Set)

	Step 1		Step 2	
	Everolimus (5 mg/day) + CP <i>n</i>=13	Everolimus (30 mg/wk) + CP <i>n</i>=13	Everolimus (5 mg/day) + CPB <i>n</i>=13	Everolimus (30 mg/wk) + CPB <i>n</i>=13
Sex, <i>n</i> (%)				
Female	5 (38.5)	6 (46.2)	8 (61.5)	6 (46.2)
Male	8 (61.5)	7 (53.8)	5 (38.5)	7 (53.8)
Age				
<65 years, <i>n</i> (%)	8 (61.5)	6 (46.2)	10 (76.9)	8 (61.5)
≥65 years, <i>n</i> (%)	5 (38.5)	7 (53.8)	3 (23.1)	5 (38.5)
Mean (SD), years	58.2 (11.13)	62.2 (13.33)	58.4 (8.51)	58.2 (13.13)
WHO PS, <i>n</i> (%)				
0	4 (30.8)	3 (23.1)	7 (53.8)	5 (38.5)
1	9 (69.2)	10 (76.9)	6 (46.2)	8 (61.5)
Stage, <i>n</i> (%)				
IIIB	2 (15.4)	3 (23.1)	1 (7.7)	1 (7.7)
IV	11 (84.6)	10 (76.9)	12 (92.3)	12 (92.3)
Histology, <i>n</i> (%)				
Adenocarcinoma	9 (69.2)	7 (53.8)	10 (76.9)	13 (100.0)
Time since diagnosis, <i>n</i> (%)				
≤6 months	9 (69.2)	12 (92.3)	13 (100)	12 (92.3)
>24 months	4 (30.8)	1 (7.7)	0	1 (7.7)
Smoking history				
Ever, <i>n</i> (%)	10 (76.9)	12 (92.3)	10 (76.9)	10 (76.9)
Current, <i>n</i> (%)	7 (53.8)	5 (38.5)	6 (46.2)	9 (69.2)
Never, <i>n</i> (%)	3 (23.1)	1 (7.7)	3 (23.1)	3 (23.1)
Mean (SD) pack years ^a	19.6 (12.28)	43.9 (35.03)	31.9 (25.86)	27.7 (19.58)

	Step 1		Step 2	
Previous therapy, ^b <i>n</i> (%)				
Radiotherapy	6 (46.2)	3 (23.1)	2 (15.4)	0
Surgery	8 (61.5)	4 (30.8)	5 (38.5)	4 (30.8)
Adjuvant chemotherapy	1 (7.7)	2 (15.4)	0	1 (7.7)

^aAmong current cigarette smokers (*n*=7 for daily everolimus + CP, 5 for weekly everolimus + CP, 6 for daily everolimus + CPB, and 8 for weekly everolimus + CPB).

^bNo patients received previous hormonal, immuno-, or targeted therapy.

CP, carboplatin and paclitaxel; CPB, carboplatin, paclitaxel, and bevacizumab; PS, performance status; SD, standard deviation; WHO, World Health Organization.

Table 3. Dose-Limiting Toxicities (Dose-Determining Population)

	Step 1		Step 2	
	Everolimus (5 mg/day) + CP <i>n</i> =12	Everolimus (30 mg/wk) + CP <i>n</i> =13	Everolimus (5 mg/day) + CPB <i>n</i> =10	Everolimus (30 mg/wk) + CPB <i>n</i> =12
≥1 DLT at any cycle, <i>n</i> (%)	8 (66.7)	9 (69.2)	9 (90.0)	9 (75.0)
Total DLTs, <i>n</i>	22	16	22	11
≥1 DLT by cycle, <i>n/N</i> (%) ^a				
Cycle 1	2/12 (16.7) ^b	4/13 (30.8) ^c	3/10 (30.0) ^d	2/12 (16.7) ^e
Cycle 2	5/12 (41.7)	1/11 (9.1)	3/10 (30.0)	1/11 (9.1)
Cycle 3	2/8 (25.0)	4/9 (44.4)	3/9 (33.3)	1/11 (9.1)
Cycle 4	2/7 (28.6)	2/6 (33.3)	4/8 (50.0)	5/8 (62.5)
Cycle 5	3/6 (50.0)	1/6 (16.7)	2/7 (28.6)	2/4 (50.0)
Cycle 6	1/3 (33.3)	1/6 (16.7)	2/5 (40.0)	0/2
Posterior end-of-cycle 1 DLT rate, mean (SD)	0.21 (0.074)	0.22 (0.072)	0.26 (0.083)	0.17 (0.062)
Probability of underdosing [0%–20%]	0.474	0.410	0.275	0.705
Probability of targeted toxicity [20%–35%]	0.475	0.537	0.586	0.289
Probability of excessive toxicity [35%–60%]	0.051	0.054	0.139	0.006
Probability of unacceptable toxicity [60%–100%]	0.000	0.000	0.000	0.000

^aNumber of patients with DLT divided by number of patients exposed to treatment during each cycle.

^bBoth patients experienced grade 3 neutropenia.

^cGrade 4 pulmonary embolism ($n=1$), grade 3 neutropenia and grade 4 myalgia ($n=1$), grade 3 neutropenia ($n=1$), grade 4 cellulitis, grade 4 febrile neutropenia, and grade 4 thrombocytopenia ($n=1$).

^dGrade 3 anal abscess ($n=1$), grade 3 neutropenia ($n=1$), and grade 4 neutropenia and grade 3 diarrhea ($n=1$).

^eGrade 4 neutropenia ($n=1$) and grade 3 thrombocytopenia ($n=1$).

CP, carboplatin and paclitaxel; CPB, carboplatin, paclitaxel, and bevacizumab; DLT, dose-limiting toxicity; SD, standard deviation.

Table 4. Adverse Events Experienced During the Core Treatment Phase (Safety Population)

	Step 1		Step 2	
	Everolimus (5 mg/day) + CP <i>n</i> =13	Everolimus (30 mg/wk) + CP <i>n</i> =13	Everolimus (5 mg/day) + CPB <i>n</i> =13	Everolimus (30 mg/wk) + CPB <i>n</i> =13
Any AE, <i>n</i> (%)	13 (100.0)	13 (100.0)	13 (100.0)	13 (100.0)
Any grade 3/4 AE, <i>n</i> (%)	12 (92.3)	11 (84.6)	12 (92.3)	12 (92.3)
Any serious AE, <i>n</i> (%)	6 (46.2)	9 (69.2)	7 (53.8)	7 (53.8)
Any AE leading to discontinuation, <i>n</i> (%)	6 (46.2)	3 (23.1)	5 (38.5)	9 (69.2)
AEs of any grade that occurred in >30% of the overall safety population, <i>n</i> (%)				
Neutropenia	11 (84.6)	10 (76.9)	11 (84.6)	10 (76.9)
Fatigue	4 (30.8)	7 (53.8)	9 (69.2)	9 (69.2)
Anemia	9 (69.2)	7 (53.8)	3 (23.1)	7 (53.8)
Thrombocytopenia	7 (53.8)	5 (38.5)	7 (53.8)	7 (53.8)
Leukopenia	9 (69.2)	6 (46.2)	6 (46.2)	4 (30.8)
Nausea	5 (38.5)	5 (38.5)	5 (38.5)	10 (76.9)
Alopecia	7 (53.8)	4 (30.8)	3 (23.1)	7 (53.8)
Stomatitis	6 (46.2)	4 (30.8)	4 (30.8)	4 (30.8)
Diarrhea	3 (23.1)	4 (30.8)	5 (38.5)	5 (38.5)
Epistaxis	2 (15.4)	0	6 (46.2)	9 (69.2)
Constipation	4 (30.8)	4 (30.8)	4 (30.8)	4 (30.8)
Peripheral neuropathy	5 (38.5)	5 (38.5)	2 (15.4)	4 (30.8)
Pain in extremity	2 (15.4)	5 (38.5)	4 (30.8)	5 (38.5)
Grade 3/4 AEs that occurred in >10% of patients in any dose schedule, <i>n</i> (%)				
Neutropenia	11 (84.6)	7 (53.8)	10 (76.9)	10 (76.9)
Leukopenia	8 (61.5)	6 (46.2)	6 (46.2)	2 (15.4)
Thrombocytopenia	4 (30.8)	1 (7.7)	4 (30.8)	3 (23.1)

	Step 1		Step 2	
Lymphopenia	1 (7.7)	2 (15.4)	5 (38.5)	2 (15.4)
Fatigue	1 (7.7)	4 (30.8)	1 (7.7)	1 (7.7)
Hypokalemia	2 (15.4)	2 (15.4)	3 (23.1)	0
Anemia	2 (15.4)	1 (7.7)	2 (15.4)	1 (7.7)
Febrile neutropenia	2 (15.4)	2 (15.4)	1 (7.7)	0
Diarrhea	0	1 (7.7)	2 (15.4)	1 (7.7)
Peripheral neuropathy	2 (15.4)	0	0	2 (15.4)
Dyspnea	0	0	0	3 (23.1)
Hypophosphatemia	1 (7.7)	2 (15.4)	0	0
Hypocalcemia	3 (23.1)	0	0	0
Pneumonia	1 (7.7)	2 (15.4)	0	0
Serious AEs that occurred in >10% of patients in any dose schedule, <i>n</i> (%)				
Febrile neutropenia	2 (15.4)	2 (15.4)	1 (7.7)	0
Leukopenia	0	2 (15.4)	1 (7.7)	1 (7.7)
Pneumonia	1 (7.7)	3 (23.1)	0	0
Pyrexia	0	4 (30.8)	0	0
Neutropenia	1 (7.7)	2 (15.4)	0	0
Lower respiratory tract infection	2 (15.4)	0	0	0

AEs of any grade, grade 3/4 AEs, and serious AEs are listed by preferred term in order of decreasing incidence over all treatment arms.

AE, adverse event; CP, carboplatin and paclitaxel; CPB, carboplatin, paclitaxel, and bevacizumab.

Table 5. Duration of Exposure and Relative Dose Intensity During the Core Treatment Phase (Safety Population)

	Step 1		Step 2	
	Everolimus (5 mg/day) + CP <i>n</i> =13	Everolimus (30 mg/wk) + CP <i>n</i> =13	Everolimus (5 mg/day) + CPB <i>n</i> =13	Everolimus (30 mg/wk) + CPB <i>n</i> =13
Duration of exposure, weeks, mean (SD) / median (range)				
Everolimus	12.1 (5.89)	11.8 (7.60)	13.9 (6.56)	11.1 (5.78)
	11.86 (3.1–21.1)	8.86 (1.9–20.9)	16.14 (0.1–21.0)	10.14 (1.0–19.3)
Carboplatin	12.7 (5.67)	12.5 (7.26)	12.2 (5.87)	13.3 (5.06)
	13.43 (3.0–21.0)	9.29 (3.0–20.9)	13.00 (3.0–21.0)	13.29 (3.0–20.4)
Paclitaxel	13.0 (5.28)	12.0 (6.86)	12.2 (5.87)	13.3 (5.08)
	13.43 (6.0–21.0)	9.29 (3.0–20.9)	13.00 (3.0–21.0)	13.29 (3.0–20.4)
Bevacizumab	NA	NA	13.0 (6.34)	13.0 (4.8)
			14.00 (3.0–21.0)	13.29 (3.0–20.4)
Any	13.0 (5.31)	12.8 (7.08)	14.1 (6.65)	13.3 (5.08)
	13.43 (6.0–21.3)	9.29 (3.0–21.0)	16.43 (3.0–21.1)	13.29 (3.0–20.4)
Relative dose intensity, mean (SD) / median (range)				
Everolimus	0.71 (0.193)	0.72 (0.168)	0.65 (0.351)	0.73 (0.243)
	0.745 (0.33–1.00)	0.750 (0.28–1.00)	0.691 (0.00–1.00)	0.750 (0.07–1.00)
Carboplatin	0.85 (0.147)	0.87 (0.107)	0.84 (0.205)	0.92 (0.160)
	0.878 (0.48–1.02)	0.893 (0.63–1.00)	0.863 (0.39–1.09)	0.898 (0.66–1.26)
Paclitaxel	0.87 (0.133)	0.88 (0.134)	0.84 (0.196)	0.92 (0.093)

	0.898 (0.52–1.00)	0.908 (0.57–1.00)	0.923 (0.51–1.01)	0.938 (0.69–1.01)
Bevacizumab	NA	NA	0.89 (0.161)	0.92 (0.141)
			0.958 (0.55–1.01)	0.975 (0.53–1.01)

CP, carboplatin and paclitaxel; CPB, carboplatin, paclitaxel, and bevacizumab; NA, not applicable; SD, standard deviation.

Table 6. Statistical Analysis of Dose Proportionality for the Daily Schedule of Everolimus (Safety Population)

	Estimate of Beta ^a	90% Confidence Interval
Step 1: Everolimus + CP		
AUC _{0–last} (ng•hr/mL)	1.66	–0.175 to 3.503
AUC _{tau} (ng•hr/mL)	1.72	–0.170 to 3.606
C _{max} (ng/mL)	1.21	–1.112 to 3.531
Step 2: Everolimus + CPB		
AUC _{0–last} (ng•hr/mL)	0.73	0.421 to 1.033
AUC _{tau} (ng•hr/mL)	0.72	0.407 to 1.035
C _{max} (ng/mL)	1.48	0.559 to 2.404

The log-transformed parameters were modeled by means of a power model of log-dose by treatment, regimen, and schedule. Samples with zero actual dose (ie, treatment interrupted or discontinued) were excluded.

^aBeta = 1 when the exposure change is exactly dose proportional.

AUC_{0–last}, area under the concentration–time curve from time 0 to the last measurable concentration sampling time; AUC_{tau}, area under the concentration–time curve over the dosing interval; C_{max}, maximum blood concentration; CP, carboplatin and paclitaxel; CPB, carboplatin, paclitaxel, and bevacizumab.

Table 7. Efficacy Outcomes (Full Analysis Set)

	Step 1		Step 2	
	Everolimus (5 mg/day) + CP <i>n</i> =13	Everolimus (30 mg/wk) + CP <i>n</i> =13	Everolimus (5 mg/day) + CPB <i>n</i> =13	Everolimus (30 mg/wk) + CPB <i>n</i> =13
Best overall response, <i>n</i> (%)				
Complete response	0	0	1 (7.7)	0
Partial response	2 (15.4)	3 (23.1)	2 (15.4)	3 (23.1)
Stable disease	6 (46.2)	6 (46.2)	5 (38.5)	6 (46.2)
Progressive disease	3 (23.1)	3 (23.1)	2 (15.4)	1 (7.7)
Unknown	2 (15.4)	1 (7.7)	3 (23.1)	3 (23.1)
Objective response rate, ^a <i>n</i> (%)	2 (15.4)	3 (23.1)	3 (23.1)	3 (23.1)
Disease control rate, ^b <i>n</i> (%)	8 (61.5)	9 (69.2)	8 (61.5)	9 (69.2)
Median PFS (95% CI), months	5.1 (1.6–8.4)	6.0 (1.4–6.2)	5.2 (1.9–NR)	9.0 (2.7–10.2)

^aPercentage of patients with a complete or partial response.

^bPercentage of patients with a complete or partial response or stable disease.

CI, confidence interval; CP, carboplatin and paclitaxel; CPB, carboplatin, paclitaxel, and bevacizumab; PFS, progression-free survival; NR, not reached.