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Erlotinib, cabozantinib, or erlotinib plus cabozantinib as second- or third-line treatment of patients with *EGFR* wild-type advanced non-small cell lung cancer (ECOG-ACRIN 1512): a phase 2 randomised controlled trial

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Author Contributions

JN was the study chair, HW was the co-chair, and SR was the thoracic group chair. JN, HW, and SR developed the concept for the study in collaboration with ECOG-ACRIN and CTEP. SD was responsible for the statistical design, development, monitoring, and analysis. JN, HW, GG, RL, JR, TO, PJS, PDS, MM and SR were investigators at the centres with the highest recruitment. SA, MB, YH and DC supervised the tissue collection, processing, and molecular and pathological examinations. JN wrote the first draft of the manuscript. All the investigators reviewed and approved the final version. A full list of the EOCG-ACRIN participating sites and investigators can be found in the appendix (page 9).

Declaration of Interests

Dr. Neal reports personal fees from Clovis, personal fees from CARET/Physicians Resource, grants and personal fees from Nektar, grants and personal fees from Boehringer Ingelheim, personal fees from ARMO BioSciences, grants from Genentech/Roche, grants from Merck, grants from ArQule, grants from Novartis, outside the submitted work.

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For the ECOG-ACRIN 1512 Investigators

Summary

Background—Erlotinib is approved for the treatment of all patients with advanced non-small cell lung cancer (NSCLC), but is most active in the treatment of *EGFR* mutant NSCLC. Cabozantinib, a small molecule tyrosine kinase inhibitor, targets MET, VEGFR, RET, ROS1, and AXL, which are implicated in lung cancer tumorigenesis. We tested the efficacy of cabozantinib and the combination of erlotinib plus cabozantinib, as compared with erlotinib, in patients with *EGFR* wild-type NSCLC.

Methods—In this three arm, randomised phase 2 study, the primary endpoint was to compare progression-free survival (PFS) of patients treated with cabozantinib versus erlotinib alone, and the combination of erlotinib plus cabozantinib versus erlotinib alone. Patients were eligible if they had received 1–2 previous treatments for advanced non-squamous *EGFR* wild-type NSCLC. Patients were stratified by performance status and line of therapy, then randomised using permuted blocks within strata to receive open label oral daily dosing of erlotinib (150 mg), cabozantinib (60 mg), or erlotinib (150 mg) and cabozantinib (40 mg). Imaging was performed every 8 weeks. At the time of radiographic progression, there was optional crossover for patients in either single

agent arm to receive combination therapy. The comparison between erlotinib and each of the arms was powered (91%) to detect a PFS hazard ratio (HR) of 0.5 (1-sided p-value 0.10-level). Secondary objectives were overall survival (OS), radiographic response by RECIST version 1.1 and description of adverse events by CTCAE version 4.0. This trial is registered with ClinicalTrials.gov, number NCT01708954.

Findings—At complete enrollment, we randomised 125 patients (42 assigned to erlotinib, 40 assigned to cabozantinib, 43 assigned to the combination), of which 111 (89%) were eligible and received treatment per protocol were included in the primary analysis (38, 38, and 35 patients on erlotinib, cabozantinib, and combination, respectively). Compared to erlotinib alone (median 1.8 months), PFS was significantly improved in the cabozantinib arm (4.3 months, HR 0.39, 1-sided p=0.0003, 80% CI 0.27–0.55) and also in the erlotinib plus cabozantinib arm (4.7 months, HR 0.37, 1-sided p=0.0003, 80% CI 0.25–0.53).

The safety analysis population included all patients who received study therapy regardless of eligibility. The most common grade 3 or 4 adverse events were diarrhea (3 [8%] in the erlotinib group vs 3 [8%] in the cabozantinib group vs 11 [28%] in the erlotinib and cabozantinib group), hypertension (none vs 10 [25%] vs 1 [3%]), fatigue (5 [13%] vs 6 [15%] vs 6 [15%]), oral mucositis (none vs 4 [10%] vs 1 [3%]), and thromboembolic event (none vs 3 [8%] vs 2 [5%]). Adverse events that were grade 3 or worse occurred in 13 (33%) patients in the erlotinib group, in 28 (70%) patients in the cabozantinib group, and in 28 (72%) patients in the erlotinib and cabozantinib group. One death of respiratory failure occurred in the cabozantinib group, deemed possibly related to either drug or disease, and one death occurred in the erlotinib plus cabozantinib group from pneumonitis. MET IHC results were available on 86 patients from the primary analysis and 85% were scored as positive (1–3+ membrane or cytoplasm staining with MET4 antibody). There was no association between MET IHC status and PFS when treated with or without cabozantinib.

Interpretation—The ECOG-ACRIN 1512 trial design tested the feasibility of using cabozantinib alone or combined with erlotinib in this patient population with *EGFR* wild-type NSCLC. Despite its modest sample size, this trial identified signals of clinically meaningful efficacy superior to that of erlotinib alone, and additional toxicity that was generally manageable. Cabozantinib-based regimens are promising for further investigation in this patient population.

Keywords

Non-small cell lung cancer; Erlotinib; Cabozantinib; Epidermal growth factor receptor

Introduction

Lung cancer remains the leading cause of cancer-related deaths worldwide, killing more than 1.3 million people annually.(1) In non-squamous non-small cell lung cancer (NSCLC), first-line chemotherapy with a platinum-based doublet for advanced disease has a historical response rate of only approximately 20–30% and a median overall survival of 8–10 months.(2) At the time of progression, second-line chemotherapeutic agents such as docetaxel and pemetrexed confer benefit with response rates of approximately 10% and progression-free survival times of approximately 3 months.(3, 4) Over the last year, immunotherapeutic

checkpoint inhibitor antibodies such as nivolumab and pembrolizumab also have been demonstrated to improve outcomes in the second line treatment of NSCLC as compared with docetaxel.(5, 6)

NSCLC adenocarcinomas can be categorized into groups by driver genomic alterations, and an overall survival benefit has been observed in patients that received appropriate targeted therapy based on genomic profiling of their tumors.(7) The most common driver is a mutation in the *EGFR* gene, present in approximately 15% of NSCLC adenocarcinomas. Erlotinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), is highly active in the treatment of tumours harboring *EGFR* mutations.(8) However, more than 75% of NSCLC adenocarcinomas have neither an EGFR mutation (described as EGFR wild-type) nor another targetable genomic alteration. In these patients, erlotinib therapy is sometimes used based on a decade-old trial, which demonstrated a 2 month survival benefit for erlotinib as compared with placebo in second and third line treatment of NSCLC.(9) This historical use of erlotinib in wild-type EGFR NSCLC formed the basis for the selection of the erlotinib control arm in this study of *EGFR* wild-type NSCLC.

Cabozantinib is an orally available TKI that is active against MET and vascular endothelial growth factor receptor-2 (VEGFR2), and also RET, ROS1, AXL, KIT, and TIE-2. MET dysregulation in non-small cell lung cancers by protein overexpression, mutations, and gene amplification can be therapeutically targeted in patients using MET inhibitors (10–12). VEGFR2 is a primary mediator of VEGF-stimulated angiogenesis, and anti-angiogenic strategies have been effective in the treatment of NSCLC. Preclinical studies have demonstrated that *MET* amplification can be a mechanism of acquired resistance to EGFR inhibitors, and that targeting both MET and EGFR synergistically inhibits proliferation of many cancer cell lines.(13, 14) Cabozantinib was selected for this study in *EGFR* wild-type NSCLC because MET protein is expressed in approximately 50% of these tumors, and anti-angiogenic therapy appears effective even in wild-type disease. (12, 15, 16) A single arm phase II study of cabozantinib had previously demonstrated that cabozantinib was active as a single agent in the treatment of NSCLC, with a response rate of 10%, disease control rate of 40% and progression-free survival of 4.2 months.(17) Another phase I/II trial showed that the combination of erlotinib and cabozantinib could safely be administered together.(18)

When this study was conceptualized, testing of tumors for *EGFR* mutations to predict sensitivity to erlotinib was the standard of care in the United States, but patients with advanced *EGFR* wild-type NSCLC refractory to chemotherapy often still received erlotinib in the second and third line setting. We conducted this trial to directly compare the efficacy of erlotinib with cabozantinib, and to compare erlotinib with cabozantinib plus erlotinib, in patients with previously treated *EGFR* wild-type advanced NSCLC. The primary objective was to determine whether single agent cabozantinib or combination therapy including cabozantinib extends progression-free survival (PFS) when compared to single agent erlotinib for this patient population. Secondary objectives were estimation of overall survival, best objective response, and toxicity. A retrospective analysis was planned to determine the association of MET expression by immunohistochemistry with outcomes.

Methods

Study design and participants

We conducted this multicenter, randomised phase II trial within the ECOG-ACRIN Cancer Research Group; accrual by institution is listed in appendix (page 9). Complete eligibility criteria are listed in the appendix (page 1). Briefly, patients were included who had metastatic or recurrent non-squamous NSCLC which had progressed following first line platinum-doublet chemotherapy, and optionally progressed following a second-line chemotherapy regimen. Patients were not allowed to have prior erlotinib or MET TKI therapy. Testing for EGFR TKI sensitizing mutations - at minimum, exon 19 deletions and L858R point mutations - was performed by local sites prior to screening for the trial, and patients with these or other known EGFR TKI sensitizing mutations were excluded. Submission of paraffin embedded tissue was required for retrospective MET testing by immunohistochemistry. Patients were required be >= 18 years old and have measurable disease by RECIST 1.1 criteria, and patients were allowed to have previously treated and stable brain metastases. Other eligibility criteria included ECOG performance status of 0–2, adequate bone marrow, renal, hepatic, and cardiac function, and no hemoptysis, tumor invasion of large vessels or organs, or recent surgery, chest irradiation, or major thrombotic events. The institutional review boards at each participating institution approved the study protocol and amendments. All patients in the trial provided written informed consent. The study complied with the Declaration of Helsinki and was done in accordance with Good Clinical Practice guidelines.

Randomisation and masking

The three treatment arms were open-label erlotinib monotherapy, cabozantinib monotherapy, and the combination of erlotinib and cabozantinib. Randomisation (1:1:1) to these arms was determined using permuted blocks within strata with dynamic balancing institutions. Randomisation was stratified by number of prior therapies (1 vs. 2) and ECOG performance status (0 *vs.* 1 *vs.* 2). Neither patients nor investigators were blinded to assigned treatment.

Procedures

Following assignment to treatment, the first dose of study drug was administered within 5 working days. Erlotinib was prescribed as standard-of-care therapy by the treating physician to patients on the erlotinib arms at a dose of 150 mg orally daily. Cabozantinib-s-malate was distributed from CTEP via the local research pharmacy and administered at a dose of 60 mg orally daily in the monotherapy arm, and 40 mg orally daily in the combination arm. Toxicity was graded according to the National Cancer Institute common toxicity terminology criteria for adverse events (NCI-CTCAE) version 4.0. Dose reduction levels for intolerable grade 2, grade 3, and grade 4 drug-related events were as follows: erlotinib: 100 mg, 50 mg; cabozantinib 40 mg, 20 mg. A maximum of 2 dose reductions or 28 day drug hold to recover from toxicity was allowed, or patients were removed from the study. Management guidelines were provided in the protocol for diarrhea, rash, and other anticipated toxicities; some toxicities allowed continuation of dose after hold, some required dose reduction, and some required permanent discontinuation.

A cycle of therapy was defined as 4 weeks. Monitoring tests for safety (complete blood count, comprehensive metabolic panel, magnesium, phosphorus, thyroid function testing, electrocardiogram) was performed every 2–4 weeks. Radiographic tumour assessment was performed at baseline and every 2 cycles (8 weeks) according to RECIST 1.1 criteria by site investigators without central image review.(19) There was no limit to length of therapy as long as patients had radiographically controlled disease and managed toxicity. At the time of radiographic progression, patients in the erlotinib or cabozantinib single agent therapy groups were allowed to crossover to combination treatment with erlotinib plus cabozantinib or discontinue treatment.

MET testing was performed in the Center for Molecular Oncologic Pathology at the Dana Farber Cancer Institute/Brigham and Women's Hospital. The laboratory was blinded as to study arm. Total MET IHC testing was performed on the Leica Bond III automated immunostainer using the Bond Refine Detection system on 4-μm sections of FFPE(formalin fixed, paraffin embedded) specimens with the rabbit polyclonal c-Met clone CVD13 (ThermoFisher Scientific, Waltham, MA, USA) and both membranous and cytoplasmic staining were scored from 0–3+ intensity, and percentage positivity, respectively.

Outcomes

The primary endpoint was progression-free survival (PFS), defined as the time from randomization to documented disease progression or death from any cause, whichever occurs first. Patients who had not experienced an event of interest by the time of analysis were censored at the date they are last known to be alive and progression-free. Overall survival was defined as the time from randomization to death from any cause, and patients who were thought to be alive at the time of final analysis were censored at the last date of contact. Best objective response was evaluated via RECIST1.1 criteria. Toxicity was determined using CTCAE v4.0 criteria. The MET outcome analysis was a pre-planned exploratory endpoint.

Statistical analysis

The primary comparison was designed to accrue and randomise 105 eligible and treated patients 1:1:1, for a total accrual of 35 patients to each of the 3 arms. After adjusting for an ineligibility rate of 10%, the total estimated sample size for randomisation was 117 patients. Using an overall one-sided 0.10 level log rank test for each comparison, this study had 91% power to detect a PFS hazard ratio of 0.50, which corresponds to an improvement in the median PFS from 2.4 months on the control arm to 4.8 months on either experimental arm. The number of PFS events needed to achieve this power for each comparison was 58 events under the alternative hypothesis. Each of the two primary comparisons of PFS used a log rank test stratified on the randomisation stratification factors with a one-sided type I error rate of 10%. PFS was defined as the time from randomisation to documented disease progression or death from any cause, whichever occurred first. Patients who had not experienced an event of interest by the time of analysis were censored at the date of the last radiographic disease assessment.

The primary endpoint was assessed in the per protocol population, which was defined as all patients who were eligible, randomly assigned, and received at least one dose of treatment. Patients were radiographically assessable if there was RECIST 1.1 measurable disease and all sites were evaluated within 4 weeks of starting therapy and a minimum of 8 weeks after starting therapy. The safety analysis population included all patients who received study therapy regardless of eligibility. MET IHC outcome analysis included the primary analysis population with tissue and MET result available. Overall survival was defined as the time from randomisation to death from any cause, and patients who were known to be alive at the time of final analysis were censored at the last date of contact. PFS and OS distributions were estimated using the Kaplan-Meier method, and Cox proportional hazards models were used to estimate the treatment hazard ratios. Response rates and toxicity were compared using Fisher's exact tests. This study was monitored by the ECOG-ACRIN Data Safety Monitoring Committee (DSMC) with one planned interim analysis for futility of PFS at roughly 50% information using the methodology of Freidlin, Korn, and Gray; at that time, if either point estimate of the PFS HR was consistent with detriment (HR > 1.0), the DSMC may have considered terminating the respective comparison early for overall lack of treatment difference.(20) The study was followed to full information, and at that time the DSMC recommended that the results be released and that patients still receiving erlotinib only be offered one of the other treatments. The software used to conduct the analyses was R version 2.10.0. This trial is registered with ClinicalTrials.gov, number NCT01708954.

Role of the funding sources

The sponsor of this trial was ECOG-ACRIN, a United States grant-funded multidisciplinary, membership-based scientific organization which was formed by the merger of the Eastern Cooperative Oncology Group (ECOG) and the American College of Radiology Imaging Network (ACRIN). ECOG-ACRIN was responsible for approving study design, development, coordinating enrollment, data collection, data management, audits, a pre-planned interim futility analysis, and the final data analysis. ECOG-ACRIN participated in the interpretation of data together with the other co-authors, and reviewed the report. SD had full access to the data, and JWN reviewed and certified the data. Bio-specimens were collected, processed and made available for correlative studies by the ECOG-ACRIN Pathology Coordinating Office and Reference Laboratory. Exelixis supplied cabozantinib for this trial through a cooperative research and development agreement (CRADA) with the National Cancer Institute Cancer Therapy Evaluation Program. The corresponding author had the final responsibility to submit for publication.

Results

Between February 7, 2013 and July 1, 2014, we completed enrollment of 125 patients and randomly assigned them to erlotinib (n=42), cabozantinib (n=40), or erlotinib plus cabozantinib (n=43). Fourteen (11%) of 125 patients never started assigned therapy or were deemed ineligible, leaving 111 (89%) patients in the primary analysis (Figure 1). At the time of data cutoff for this analysis, August 31, 2015, 33 (30%) patients in the primary analysis population were alive. The median follow-up was 17.0 months (15.4 months for erlotinib, 23.4 months for cabozantinib, and 14.9 months for erlotinib plus cabozantinib, with

interquartile range for all groups of 12.7 – 23.1 months). Patient demographics and disease characteristics were generally balanced (table 1) with the exception of ethnicity, history of brain metastases, mediastinal metastases (p=0.03), and prior immunotherapy.

Exposure to therapy was assessed for each group. The median number of cycles received by treatment group were: 2 cycles for erlotinib (range: 1–10); 3 cycles for cabozantinib (range: 1–17); and 2 cycles for erlotinib plus cabozantinib (range: 1–15). Planned or unplanned dose modifications were experienced by 29 (76%) of 38 eligible and treated patients in the erlotinib group; 36 (95%) of 38 in the cabozantinib group; and 34 (97%) of 35 in the erlotinib plus cabozantinib group. The data collected did not capture the reason for dose modification, although the protocol only permitted dose modification due to adverse events, not at investigator's discretion, The average daily dose of erlotinib was 140.2 mg of erlotinib for the erlotinib group and 125.5 mg of erlotinib for the erlotinib plus cabozantinib group. The average daily dose of cabozantinib was 52.6 mg for the cabozantinib group and 31.7 mg for the erlotinib plus cabozantinib group.

Table 2 summarizes the efficacy results. Progression-free survival was statistically significantly better in the cabozantinib group than in the erlotinib group (HR=0.39, 80% CI [0.27–0.55], 1-sided p=0.0003); it was also better in the cabozantinib plus erlotinib group than in the erlotinib group (HR=0.37, 80% CI [0.25–0.53], 1-sided p=0.0003). Multivariable Cox models were fitted to adjust for imbalanced baseline variables and prognostic factors, and results were consistent with the unadjusted model. The estimated median PFS and corresponding 95% CI on each treatment arm was 1.8 months (1.7–2.2 months) on erlotinib, 4.3 months (3.6–7.4 months) on cabozantinib, and 4.7 months (2.4–7.4 months) on erlotinib plus cabozantinib. Figure 2A displays PFS by treatment arm. Overall survival was also better in the cabozantinib group than in the erlotinib group (HR=0.68, 80% CI [0.49–0.95], 1-sided p=0.07); it was statistically significantly better in the cabozantinib plus erlotinib group than in the erlotinib group (HR=0.51, 80% CI [0.35–0.74], 1-sided p=0.01). The estimated median OS and corresponding 95% CI on each treatment arm was 5.1 months (3.3–9.3 months) on erlotinib, 9.2 months (5.1–15.0 months) on cabozantinib and 13.3 months (7.6-NA months) on erlotinib plus cabozantinib. Figure 2B displays overall survival by treatment arm. Response rate was measured using RECIST 1.1 criteria, and objective responses did not differ significantly between the groups (Table 2). There was one partial response (PR) in the erlotinib group with a 48% reduction in tumor, four PRs in the cabozantinib group with median reduction of 36% (range 30–53%), and one PR in the erlotinib plus cabozantinib group with a 33% reduction in tumor. A total of 19 (17%) of 111 patients from the monotherapy arms crossed over to start combination therapy: 13 (34%) of 38 crossed over from erlotinib, and 6 (16%) of 38 crossed over from cabozantinib. No radiographic responses (complete response or PR) were observed in patients who crossed over to combination chemotherapy.

Tissue samples were collected on all patients at baseline for central MET IHC testing. Membranous and cytoplasmic staining were individually scored, and positivity was declared if MET was expressed in either the membrane or cytoplasm. A total of 107 independent patient samples were tested. Twelve samples were excluded from the analysis due to no sufficient tumor tissue available for scoring. From the 95 remaining samples, 86 came from

the primary analysis population of eligible and treated patients. The overall of MET positivity in tissue samples was 73 (85%) of 86; by group it was 24 (80%) of 30 on erlotinib, 26 (81%) of 32 on cabozantinib, and 23 (96%) of 24 on erlotinib plus cabozantinib. Per protocol, we combined the cabozantinib treated groups for this analysis. MET status was not a significant predictor of PFS in a model also adjusted for whether or not a patient received cabozantinib: the estimated PFS HR for MET positivity was 0.65 (2-sided p=0.19). Progression-free survival by MET status is displayed in figure 3. The median PFS among MET-negative patients randomised to erlotinib was 1.9 months (95% CI: 1.7 months - NR); for MET-negative patients who received any cabozantinib it was 4.4 months (95% CI: 1.8 months - NR). The median PFS among MET-positive patients randomised to erlotinib was 1.8 months (95% CI: 1.6–2.9 months); for MET-positive patients who received any cabozantinib it was 5.0 months (95% CI: 3.9–7.4 months). Testing of additional MET positive cutpoints (cytoplasmic, membranous, or either) did not demonstrate that these were a significant predictor of PFS either (data not shown).

Adverse events

Selected adverse events of interest are presented in Table 3, and all treatment-related adverse events are presented in the appendix (page 3). The most common grade 3 or 4 adverse events were diarrhea (3 [8%] in the erlotinib group vs 3 [8%] in the cabozantinib group vs 11 [28%] in the erlotinib and cabozantinib group), hypertension (none vs 10 [25%] vs 1 [3%]), fatigue (5 [13%] vs 6 [15%] vs 6 [15%]), oral mucositis (none vs 4 [10%] vs 1 [3%]), and thromboembolic event (none vs 3 [8%] vs 2 [5%]). Hypertension was significantly higher in the cabozantinib group compared with the erlotinib group (2-sided p=0.001), as was diarrhea in the erlotinib plus cabozantinib group compared with the erlotinib group (2-sided p=0.02). Adverse events of grade 3 or worse occurred in 13 (33%) patients in the erlotinib group, and were significantly higher in the cabozantinib group (28 patients [70%], 2-sided p=0.001), and in the erlotinib and cabozantinib group (28 patients [72%], 2-sided p=0.002). In the erlotinib group, 3 patients discontinued treatment for adverse events, compared with 11 patients in the cabozantinib group, and 13 patients in the erlotinib and cabozantinib group. Deaths on or within 30 days of last dose of treatment included 7 (17%) in the erlotinib group, 3 (8%) in the cabozantinib group, and 7 (16%) in the cabozantinib plus erlotinib group, and are presented in the appendix (page 8). All were deemed unlikely or unrelated to treatment, except for two: one death due to respiratory failure in the cabozantinib group, deemed possibly related to either drug or disease, and one death in the erlotinib plus cabozantinib group from drug pneumonitis due to either agent or the combination.

Discussion

Our findings show that cabozantinib treatment alone, or cabozantinib plus erlotinib, was associated with a statistically significant improvement in progression-free survival when compared to erlotinib alone in patients with *EGFR* wild-type NSCLC who progressed after prior therapy. This treatment effect was supported by a corresponding improvement in overall survival, albeit with an increase in toxicity.

The results for the control arm were consistent with other trials using erlotinib in *EGFR* wild-type patients. During the conduct of this study, other trials were reported that used erlotinib as a control arm in *EGFR* wild-type NSCLC, in comparison to second line single agent chemotherapy. In the Italian TAILOR trial, 222 patients were randomised to erlotinib or docetaxel.(21) Median overall survival was 8.2 months with docetaxel, compared with 5.4 months with erlotinib (adjusted hazard ratio (HR) 0.73, 95% CI 0.53–1.00; p=0.05), and median progression-free survival (PFS) was 2.9 months with docetaxel versus 2.4 months with erlotinib (adjusted HR 0.71, 95% CI 0.53–0.95; p=0.02). In the Japanese DELTA trial, 301 patients were randomly assigned to erlotinib or docetaxel. (22) In a subset analysis of 199 patients with *EGFR* wild-type tumors, OS for erlotinib versus docetaxel was 9.0 v 10.1 months (HR, 0.98; 95% CI, 0.69 to 1.39; P = 0.91), and PFS for erlotinib versus docetaxel was 1.3 versus 2.9 months (HR, 1.45; 95% CI, 1.09 to 1.94; P = 0.01). The phase 3 TITAN study randomised 424 patients to erlotinib versus docetaxel or pemetrexed chemotherapy. (23) No differences in OS or PFS were identified between the groups, even for the *EGFR* wild-type subgroup, although *EGFR* mutation status was indeterminate or missing on more than half of patients. Overall, these studies consistently observe modest efficacy of erlotinib in *EGFR* wild-type NSCLC, and suggest inhibiting other non-EGFR signaling pathways is a rational treatment strategy in this subgroup of patients. Our observed median PFS of 1.8 months was similar to the 1.3, 1.4, and 2.4 months observed on the DELTA, TITAN, and TAILOR trials, respectively. Our observed median OS of 5.1 months was similar to the 5.3 and 5.4 months observed on the TITAN and TAILOR trials, but less than the 9.0 months observed in the DELTA trial. In addition, the PFS on the cabozantinib monotherapy arm of 4.3 months was quite similar to the 4.2 months previously observed in the previously conducted single arm phase II study of cabozantinib, and OS on this study was not reported. Therefore, the favorable efficacy outcomes observed in both experimental arms in our study are both clinically and statistically significant.

Cabozantinib therapy, or the combination of cabozantinib and erlotinib, was associated with an increased occurrence of grade 3 or worse adverse events compared with erlotinib alone. Many of these adverse events were symptomatic, such as fatigue, nausea, oral mucositis, and palmar-plantar erythrodysesthesia syndrome, all more frequently associated with cabozantinib treatment. The previous phase I/II trial of erlotinib and cabozantinib demonstrated that cabozantinib needed to be reduced to 40 mg daily in combination with erlotinib to limit diarrhea; despite this, patients still received an average of 32 mg of cabozantinib daily on the combination arm. While not statistically imbalanced for this randomised trial, the fatal adverse events of respiratory failure and pneumonitis, and life threatening adverse events of intracranial hemorrhage, thromboembolic event, other skin disorder, and thrombocytopenia were only observed on the cabozantinib arms. This suggests that cabozantinib is potentially less tolerable than erlotinib, though given its more potent clinical benefit this may be a worthwhile tradeoff. The recent FDA approval of cabozantinib 60 mg daily for renal cell carcinoma suggests that it has an acceptable overall safety profile as monotherapy.

Given the potential mechanism of action as a MET inhibitor, it was hypothesized that MET protein expression might be predictive of response to cabozantinib. However, no effect was observed on PFS by MET status in the subset of patients in whom MET IHC testing and

response assessment was available. Additionally, cabozantinib is known to inhibit AXL, which may be activated together with other driver tyrosine kinases. While there is no standardized assay for AXL expression, a biomarker may be identified in an ongoing clinical trial of cabozantinib that includes patients with NSCLC that has increased AXL activity (NCT01639508). Cabozantinib also may be exerting its clinical benefit as a VEGFR2 inhibitor. It is known that VEGFR2 inhibition is effective in the second line treatment of NSCLC, as a VEGFR2 monoclonal antibody, ramucirumab, is FDA approved in combination with docetaxel based on a median overall survival of 10.5 months compared with 9.1 months for docetaxel alone (HR 0.86, 95% CI [0.75–0.98]; p=0.023).(15) Additionally, the small molecule VEGFR2 inhibitor nintedanib plus docetaxel is active in patients with adenocarcinoma histology, with a median overall survival of 12.6 months versus 10.3 months for docetaxel alone (HR 0.83 [95% CI 0.70–0.99], p=0.0359), which led to approval by European regulatory agencies (24). However, no broadly validated predictive biomarker of anti-angiogenic therapy has been identified to date.

Limitations of this study include the modest sample size and the lack of detailed molecular driver oncogene characterization. Although effects on overall survival were observed, a larger trial would be needed to confirm these results. However, conducting a larger trial of similar design would be challenging. We believe that erlotinib is no longer a suitable control arm for a confirmatory trial given the mounting evidence that erlotinib is minimally effective in an EGFR wild-type NSCLC population. One potential comparator would be docetaxel, with a median PFS of 3.0 months and median OS of 9.1 months in a recent large randomised trial.(15) Another potential comparison therapy would be nivolumab, which was superior to docetaxel in non-squamous NSCLC for median OS (12.2 months for nivolumab vs 9.4 months for docetaxel) but not median PFS (2.3 months for nivolumab vs 4.2 months for docetaxel). However, with numerical medians of PFS and OS similar to those we observed for cabozantinib, it appears unlikely that cabozantinib monotherapy would be superior to either docetaxel or nivolumab in a randomised trial. Another limitation is that we only collected known KRAS driver oncogene status, and limited tissue exists to pursue further testing which has become a standard of care in the intervening years since the study began. It is possible that potential cabozantinib sensitive molecular drivers such as RET rearrangement, ROS1 rearrangement, and *MET* amplification or *MET* exon 14 skipping mutation were imbalanced between the groups, leading to the observed survival benefits of cabozantinib. This is unlikely, because we would predict all of these to total no more than 10% of this study population, and patients with these alterations would be expected to have radiographic responses to targeted therapy. Few such responses were observed on this trial, even in the cabozantinib groups, suggesting that individual patients with particularly sensitive disease were unlikely to be imbalanced across the arms. Therefore, it is unlikely that a small subgroup with particular molecular driver alterations was responsible the observed clinical benefit of cabozantinib, though testing of remaining tissue is of interest.

To our knowledge, ECOG-ACRIN 1512 is the first randomised study to show that cabozantinib, either alone or in combination with erlotinib, improved progression-free survival and overall survival compared with single agent erlotinib in *EGFR* wild-type NSCLC in the 2nd and 3rd line setting. Despite the increased toxicity profile, this suggests that cabozantinib is worthy of further study in this patient population. ECOG-ACRIN

investigators plan to initiate a follow-up study to build on these observations and further delineate a role for cabozantinib in the treatment of advanced non-squamous NSCLC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Research in Context

Evidence before this study

In developing the study design and protocol, we did a systematic review of the scientific literature. We searched PubMed, with no time restrictions; abstracts of major oncology meetings; and trial websites including ClinicalTrials.gov, for preclinical data and clinical trials assessing chemotherapy in patients with lung cancer, EGFR therapies in these patients, MET inhibitor therapies in these patients, and the combination of these methods. Search terms included “non-small cell lung cancer”, “EGFR”, and “MET”.

Clinical data in support of this trial included a phase 2 study cabozantinib in patients with previously treated NSCLC which showed that it was active in generating objective tumour responses and meaningful time to progression of disease. Additionally a phase 1/2 trial of erlotinib and cabozantinib demonstrated the safety of the combination of these drugs. Based on our review of the literature and discussions with clinicians, researchers, and regulatory bodies, we postulated that combining erlotinib with cabozantinib might improve treatment efficacy in patients with previously treated *EGFR* wild-type advanced non-squamous non-small cell lung cancer.

Added value of this study

Our study shows significant improvement in progression-free survival in patients who were treated with cabozantinib, or the combination of cabozantinib and erlotinib, as compared with erlotinib alone. There was also a signal of improvement in overall survival observed in these groups. We found no evidence of associate of progression-free survival with MET status as determined by immunohistochemical staining.

Implications of all the available evidence

The ECOG-ACRIN 1512 trial design tested the feasibility of using cabozantinib alone or combined with erlotinib in this patient population with *EGFR* wild-type NSCLC. Despite its modest sample size, this trial identified signals of clinically meaningful efficacy superior to that of erlotinib alone, and additional toxicity that was generally manageable. Further investigation of cabozantinib in this patient population, potentially in combination with other established therapies, is warranted.

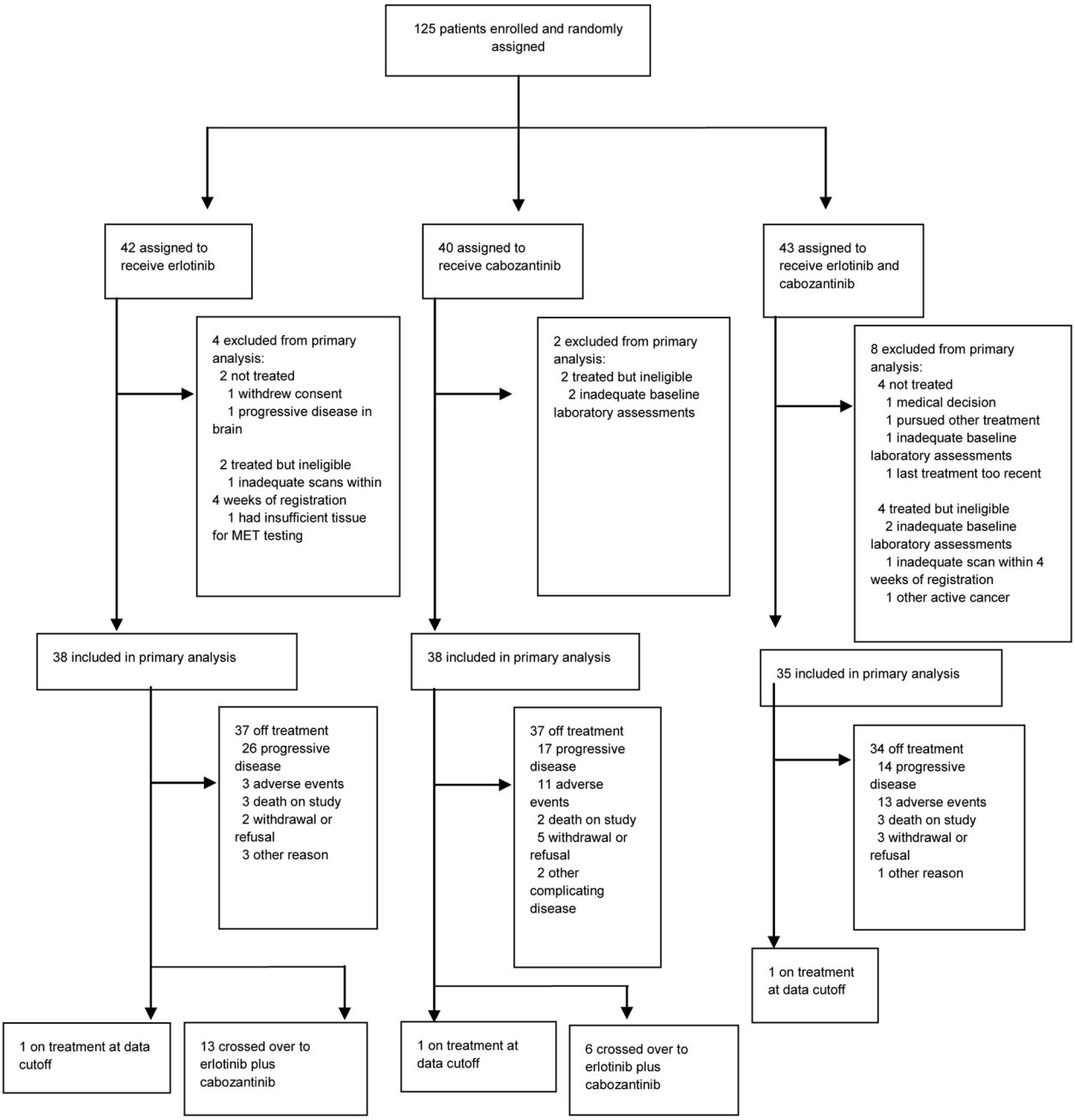
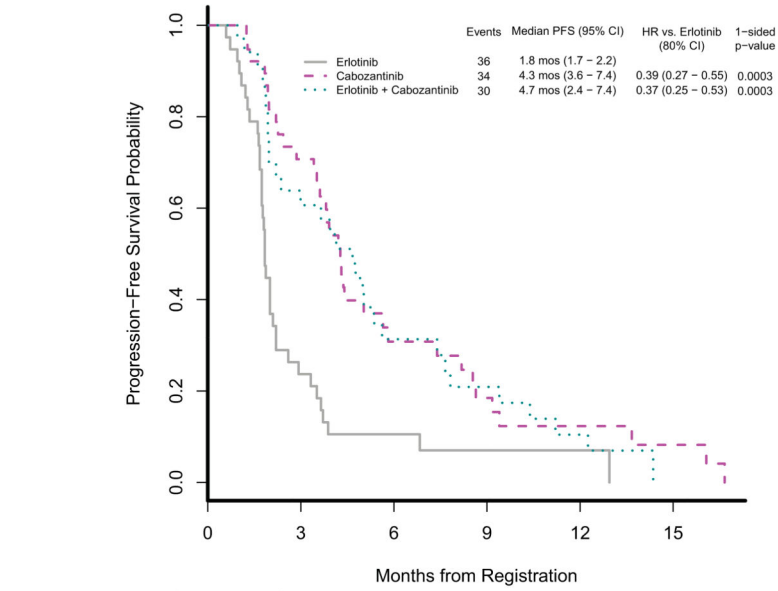


Figure 1.
Trial profile



Number at risk (number censored)						
Erlotinib	38 (0)	9 (0)	3 (1)	2 (1)	1 (2)	0 (2)
Cabozantinib	38 (0)	26 (1)	10 (3)	6 (3)	4 (3)	2 (4)
Erlotinib + Cabozantinib	35 (0)	19 (3)	9 (4)	6 (4)	3 (4)	0 (5)

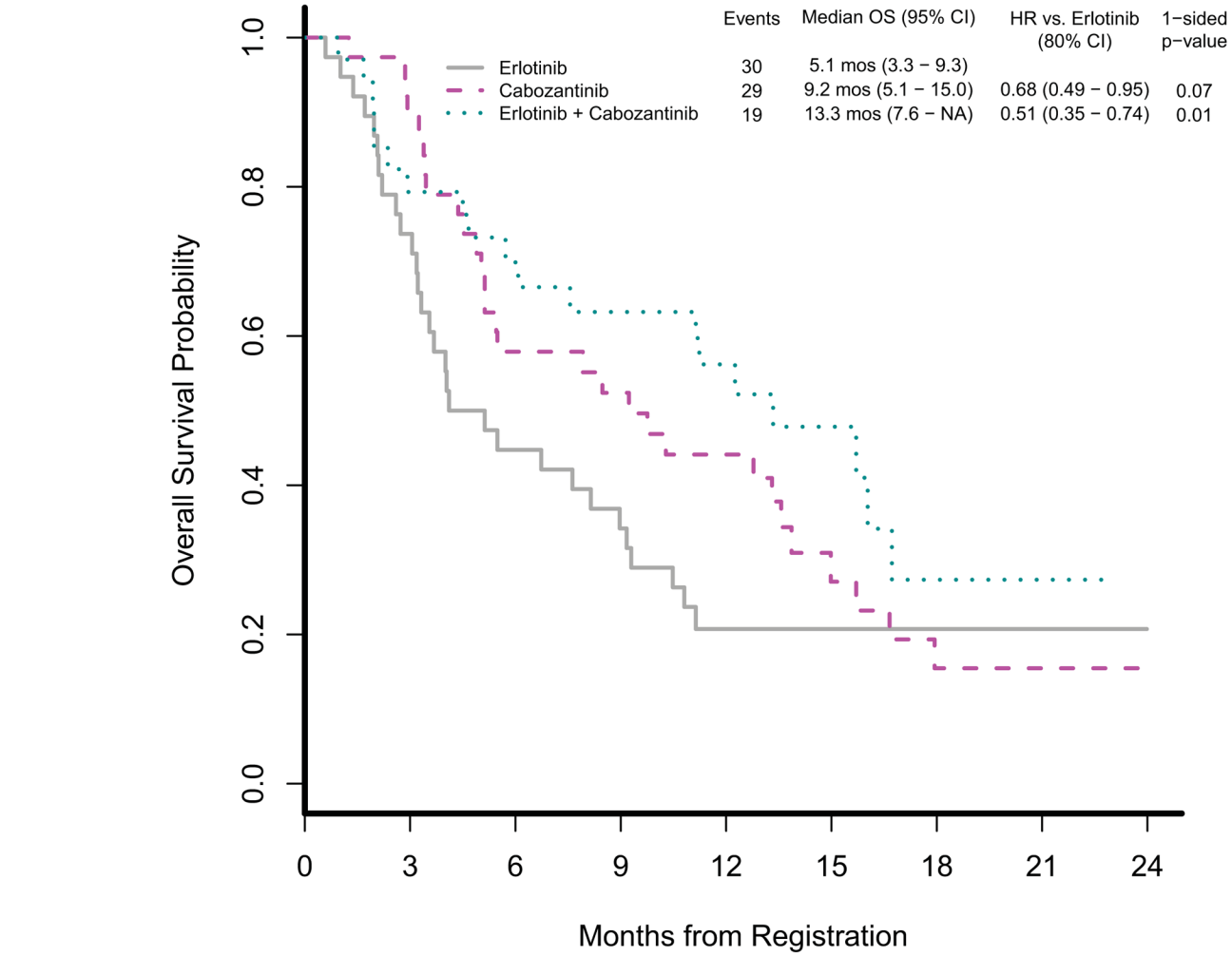
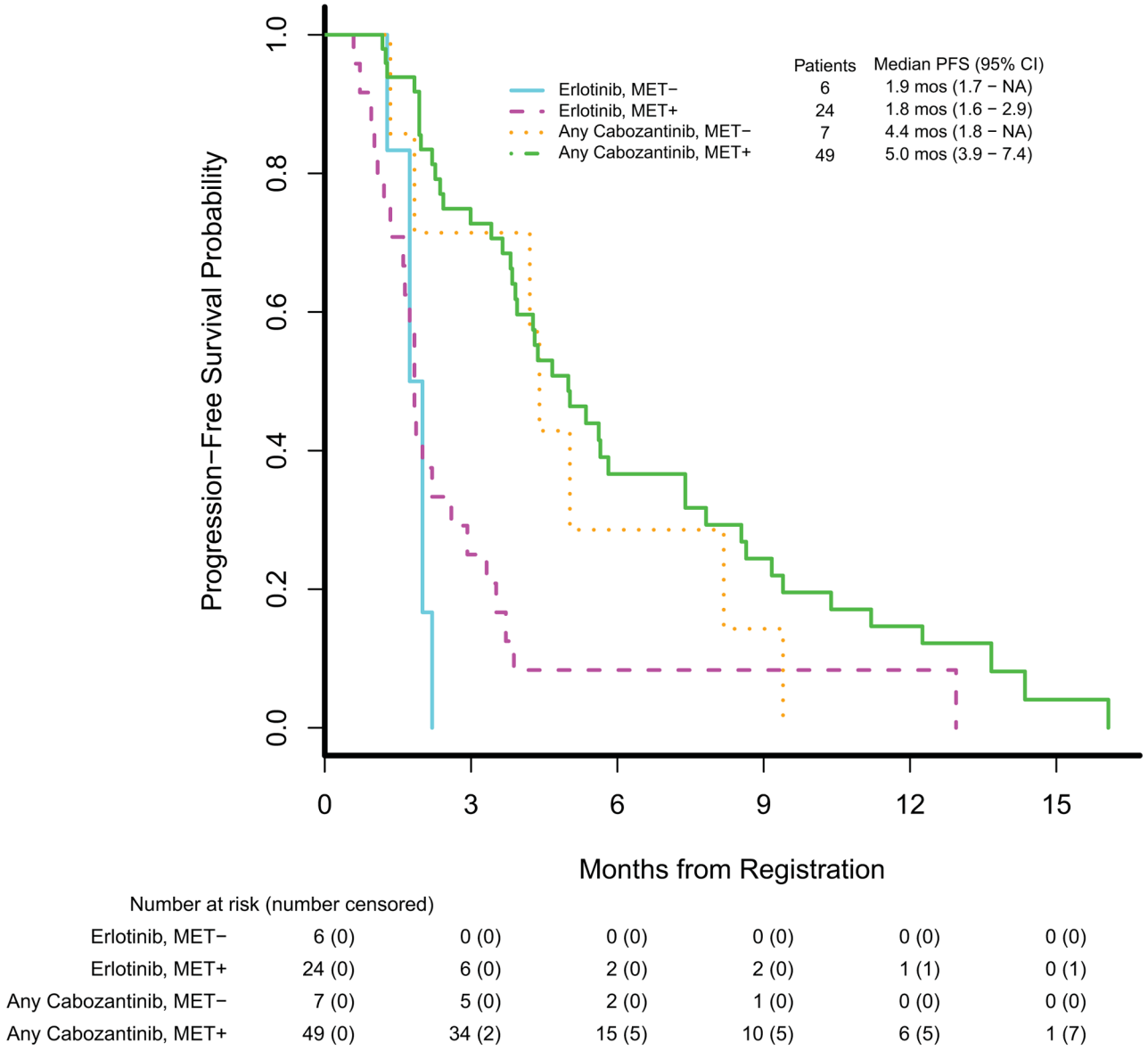


Figure 2.

Kaplan-Meier estimates of progression-free survival and overall survival

(A) Progression-free survival and (B) overall survival (OS) in the treatment per protocol population. HR=hazard ratio.



Number at risk (number censored)						
Erlotinib, MET−	6 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Erlotinib, MET+	24 (0)	6 (0)	2 (0)	2 (0)	1 (1)	0 (1)
Any Cabozantinib, MET−	7 (0)	5 (0)	2 (0)	1 (0)	0 (0)	0 (0)
Any Cabozantinib, MET+	49 (0)	34 (2)	15 (5)	10 (5)	6 (5)	1 (7)

Figure 3.

Kaplan-Meier estimates of progression-free survival (PFS) by MET IHC status (positive vs. negative) and cabozantinib exposure (any or none).

Table 1

Baseline characteristics

Variable	Category	Erlotinib	Cabozantinib (60mg)	Erlotinib + Cabozantinib (40mg)	Total
Total		38	38	35	111
Sex	Female	20 (53)	24 (63)	17 (49)	61 (55)
	Male	18 (47)	14 (37)	18 (51)	50 (45)
Age	Mean (Std Dev)	66.3 (9.8)	65.9 (10.1)	63.5 (9.0)	65.3 (9.6)
PS	0	9 (24)	9 (24)	8 (23)	26 (23)
	1	24 (63)	25 (66)	23 (66)	72 (65)
	2	5 (13)	4 (11)	4 (11)	13 (12)
Weight Loss	<5%	30 (79)	29 (76)	27 (77)	86 (77)
	>= 20%	0 (0)	1 (3)	0 (0)	1 (1)
	10 to <20%	1 (3)	3 (8)	5 (14)	9 (8)
	5 to <10%	7 (18)	5 (13)	3 (9)	15 (14)
Ethnicity	Hispanic/Latino	0 (0)	0 (0)	2 (6)	2 (2)
	Not Hispanic/Latino	38 (100)	38 (100)	32 (91)	108 (97)
	Not Reported	0 (0)	0 (0)	1 (3)	1 (1)
Race	American Indian	2 (5)	1 (3)	0 (0)	3 (3)
	Asian	2 (5)	0 (0)	0 (0)	2 (2)
	Black	2 (5)	3 (8)	2 (6)	7 (6)
	Native Hawaiian	0 (0)	1 (3)	0 (0)	1 (1)
	White	32 (84)	33 (87)	31 (89)	96 (86)
	Not Reported	0 (0)	0 (0)	2 (6)	2 (2)
Smoking status	Current	8 (21)	9 (24)	8 (23)	25 (23)
	Former	25 (66)	23 (61)	21 (60)	69 (62)
	Never	5 (13)	6 (16)	6 (17)	17 (15)
Stage	IV M1a	8 (21)	6 (16)	5 (14)	19 (17)
	IV M1b	21 (55)	18 (47)	20 (57)	59 (53)
	Recurrent	9 (24)	14 (37)	10 (29)	33 (30)
Histology	Adenocarcinoma	35 (92)	36 (95)	32 (91)	103 (93)

Variable	Category	Erlotinib	Cabozantinib (60mg)	Erlotinib + Cabozantinib (40mg)	Total
	Combined/mixed	0 (0)	0 (0)	0 (0)	0 (0)
	Large cell	1 (3)	2 (5)	0 (0)	3 (3)
	NSCLC NOS	2 (5)	0 (0)	2 (6)	4 (4)
	Other	0 (0)	0 (0)	1 (3)	1 (1)
Multi-agent systemic chemotherapy		36 (95)	38 (100)	34 (97)	108 (97)
Single agent systemic chemotherapy		23 (61)	17 (45)	13 (37)	53 (48)
Immunotherapy		2 (5)	2 (5)	8 (23)	12 (11)
Radiation		20 (53)	22 (58)	23 (66)	65 (59)
Surgery		8 (21)	17 (45)	11 (31)	36 (32)
Maintenance chemotherapy	None	9 (24)	15 (39)	15 (43)	39 (35)
	Continuation	23 (61)	17 (45)	14 (40)	54 (49)
	Switch	6 (16)	6 (16)	6 (17)	18 (16)
Second line chemotherapy received		15 (39)	15 (39)	14 (40)	44 (40)
EGFR status	Wild-type	37 (97)	37 (97)	33 (94)	107 (96)
	Inconclusive	1 (3)	0 (0)	2 (6)	3 (3)
	Not done	0 (0)	1 (3)	0 (0)	1 (1)
KRAS status	Positive	4 (11)	7 (18)	3 (9)	14 (13)
	Wild-type	7 (18)	11 (29)	5 (14)	23 (21)
	Inconclusive	1 (3)	0 (0)	2 (6)	3 (3)
	Not done	26 (68)	20 (53)	25 (71)	71 (64)
Brain metastasis, history		3 (8)	13 (34)	9 (26)	25 (23)
Brain metastasis, treatment	Gam. knife/Radiosx.	2 (67)	7 (54)	4 (44)	13 (52)
	Surgery	0 (0)	0 (0)	1 (11)	1 (4)
	WBRT	1 (33)	6 (46)	4 (44)	11 (44)
Mediastinal metastasis		11 (29)	22 (58)	17 (49)	50 (45)
Pleura metastasis		5 (13)	3 (8)	4 (11)	12 (11)
Liver metastasis		10 (26)	10 (26)	9 (26)	29 (26)
Adrenal metastasis		5 (13)	6 (16)	7 (20)	18 (16)
Bone metastasis		13 (34)	10 (26)	14 (40)	37 (33)

Variable	Category	Erlotinib	Cabozantinib (60mg)	Erlotinib + Cabozantinib (40mg)	Total
Pleural effusion		9 (24)	9 (24)	7 (20)	25 (23)

Table 2

Efficacy endpoints

	Erlotinib (n=38)	Cabozantinib (n=38)	Erlotinib plus Cabozantinib (n=35)
Progression-free survival			
Deaths or disease progression	36 (95%)	34 (89%)	30 (86%)
Median progression-free survival, months (95% CI)	1.8 (1.7–2.2)	4.3 (3.6–7.4)	4.7 (2.4–7.4)
Overall survival			
Deaths	30 (79%)	29 (76%)	19 (54%)
Median overall survival, months (95% CI)	5.1 (3.3–9.3)	9.2 (5.1–15.0)	13.3 (7.6-NR)
Best overall response			
Complete response	0	0	0
Partial response	1 (3%)	4 (11%)	1 (3%)
Stable disease	6 (16%)	19 (50%)	16 (46%)
Progressive disease	25 (66%)	9 (24%)	8 (23%)
Not evaluable/not assessed	6 (16%)	6 (16%)	10 (29%)

Data are n (%) unless otherwise indicated. NR = not reached

Table 3

Adverse events of interest

	Erlotinib (n=40)				Cabozantinib (n=40)				Erlotinib + Cabozantinib (n=39)			
	Gr 1–2	**Gr 3**	**Gr 4**	**Gr 5**	**Gr 1–2**	**Gr 3**	**Gr 4**	**Gr 5**	**Gr 1–2**	**Gr 3**	**Gr 4**	**Gr 5**
Diarrhea	21 (53%)	3 (8%)	0	0	20 (50%)	3 (8%)	0	0	25 (64%)	11 (28%)	0	0
Acneiform rash	22 (55%)	1 (3%)	0	0	6 (15%)	1 (3%)	0	0	23 (59%)	2 (5%)	0	0
Fatigue	18 (45%)	5 (13%)	0	0	22 (55%)	6 (15%)	0	0	27 (69%)	6 (15%)	0	0
Anorexia	10 (25%)	2 (5%)	0	0	15 (38%)	1 (3%)	0	0	17 (44%)	3 (8%)	0	0
Nausea	8 (20%)	1 (3%)	0	0	18 (45%)	2 (5%)	0	0	17 (44%)	1 (3%)	0	0
Oral mucositis	2 (5%)	0	0	0	13 (33%)	4 (10%)	0	0	8 (21%)	1 (3%)	0	0
Palmar-plantar erythrodysesthesia syndrome	3 (8%)	0	0	0	6 (15%)	1 (3%)	0	0	6 (15%)		0	0
Hypothyroidism		0	0	0	10 (25%)	0	0	0	2 (5%)	0	0	0
Aspartate aminotransferase increased	8 (20%)	0	0	0	26 (65%)	0	0	0	17 (44%)	0	0	0
Hypertension	4 (10%)	0	0	0	8 (20%)	10 (25%)	0	0	17 (44%)	1 (3%)	0	0
Thromboembolic event	2 (5%)	0	0	0	1 (3%)	3 (8%)	0	0	0	1 (3%)	1 (3%)	0
Intracranial hemorrhage	0	0	0	0	0	0	1 (3%)	0	0	0	0	0
Pneumonitis	1(3%)	0	0	0	0	0	0	0	0	0	0	1 (3%)
Respiratory failure	0	0	0	0	0	0	0	1 (3%)	0	0	0	0
Worst degree toxicity	23 (58%)	13 (33%)	0	0	12 (30%)	26 (65%)	1 (3%)	1 (3%)	11 (28%)	24 (62%)	3 (8%)	1 (3%)

Data are n (%). The table shows selected adverse events of interest possibly related to study treatment. All treatment-related adverse events are presented in the appendix (page 3).