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Randomized phase 2 study of maintenance linsitinib (OSI-906) in combination with erlotinib compared with placebo plus erlotinib after platinum-based chemotherapy in patients with advanced non–small cell lung cancer

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Abstract

Background: Maintenance therapy is important in advanced/metastatic non–small cell lung cancer (NSCLC). Erlotinib as switch maintenance following platinum-based chemotherapy increases survival. Epidermal growth factor receptor and the insulin-like growth factor receptor (IGFR) pathway cross-talk mediates resistance to individual receptor blockade. This study compared maintenance linsitinib plus erlotinib vs erlotinib plus placebo in NSCLC patients.

Methods: In this Phase II randomized trial, patients without progression following four cycles of first-line platinum-based chemotherapy received continuous schedule maintenance oral linsitinib 150 mg or placebo BID combined with erlotinib 150 mg QD for 21-day cycles. The primary endpoint was progression-free survival (PFS).

Results: The study was unblinded early due to linsitinib non-superiority. No difference was found between the two treatment groups in median PFS of 125 days linsitinib vs 129 days placebo (P=0.601); no difference in overall survival (OS) was observed. Tolerability was similar, although in the linsitinib-group, treatment-related adverse events and discontinuations were more frequent. No drug-drug interaction was implicated.

Conclusions: Linsitinib maintenance therapy added to erlotinib did not improve PFS or OS in non-progressing NSCLC patients. This highlights the need for robust biomarkers of response for combinations that incorporate IGFR targeted therapies in maintenance or other therapeutic settings.

Introduction

An estimated 1.8 million new cases and 1.6 million deaths in 2012 were attributed to lung cancer, the most common cancer worldwide (Torre *et al*, 2015). Non–small cell lung cancer (NSCLC) accounts for approximately 85%–90% of lung cancer cases, the majority of which are advanced or metastatic with poor prognosis and limited treatment options. Although treatment options for NSCLC have been advanced by the introduction of molecularly targeted agents that inhibit activating driver variants in genes such as *ALK*, *EGFR*, and *ROS1* (Paez *et al*, 2004; Rosell *et al*, 2009; Rothschild, 2015), standard-of-care first-line therapy in patients who do not harbor targetable mutations typically consists of four to six cycles of platinum doublet therapy (Manegold, 2014).

Following progression on first-line therapy, options are limited, with only about 50%–60% of patients able to receive second-line therapy because of declining performance status (Manegold, 2014). Therefore, an important option to prolong the clinical benefit obtained by first-line platinum-containing chemotherapy is the use of maintenance therapy until disease progression or unacceptable toxicity. Maintenance therapy can either be continuation maintenance of first-line therapy or a switch to a different agent after four cycles of platinum therapy (switch-maintenance) (Zhang *et al*, 2015; Genestreti *et al*, 2015). Agents used in continuation maintenance chemotherapy include pemetrexed (Paz-Ares *et al*, 2013), bevacizumab (Sandler *et al*, 2006), and, arguably, gemcitabine (Perol *et al*, 2012), or a combination of bevacizumab and gemcitabine (Patel *et al*, 2013). Switch maintenance agents include chemotherapeutic agents such as pemetrexed (Ciuleanu, 2009), as well as targeted agents such as erlotinib (Cappuzzo *et al*, 2010; Perol *et al*, 2012) and gefitinib (Zhang *et al*, 2012). Maintenance therapy has yielded

improvements in overall survival (OS) and progression-free survival (PFS) in some studies. Specifically, switch therapy to a new type of agent (either epidermal growth factor receptor-tyrosine kinase inhibitors [EGFR-TKIs] or chemotherapy) may decrease chemotherapy resistance (Genestreti *et al*, 2015). The extent of improvement varies, however, with the type of maintenance therapy and the patient population (Zhou *et al*, 2015; Lu *et al*, 2015; Zhang *et al*, 2015).

Erlotinib, an EGFR TKI used for first-line therapy in NSCLC patients with sensitizing mutations (Melosky, 2014), has demonstrated statistically significant, though modest, increases in PFS (3.0 vs 2.8 months) and OS (12.0 vs 11.0 months) compared with placebo when used as switch maintenance after four cycles of platinum-based chemotherapy in a randomized, Phase III clinical trial (Cappuzzo *et al*, 2010). In most patients, however, erlotinib resistance is an eventual occurrence, either from primary resistance or as acquired resistance via secondary *EGFR* mutations (eg, T790M mutation in exon 20) or alterations in alternative pathways (e.g., MET, human epidermal growth factor 2 [HER2], *BRAF*) (Stewart *et al*, 2015; Chung, 2015).

The insulin-like growth factor 1 (IGF-1) signaling pathway is involved in tumor cell proliferation, survival, and invasiveness, and shares downstream signaling pathways (such as MAPK and PI3K) with EGFR (Fidler *et al*, 2012; Stewart *et al*, 2015). Studies have shown that increased activity of insulin-like growth factor 1 receptor (IGF-1R) leads to tumorigenesis. IGF-1R is aberrantly expressed in tumors, and its overexpression is associated with decreased survival in several tumor types, including NSCLC (Pollack, 2012; King *et al*, 2014; Kim *et al*, 2014). Furthermore, acquired resistance to reversible EGFR TKIs has been reported in NSCLC

cells engaging this pathway, while an IGF1-R inhibitor in combination with erlotinib suppressed the emergence of TKI-resistance (Sharma *et al*, 2010).

As such, IGF-1R has developed into an important target for NSCLC treatment, particularly in combination with EGFR inhibitors like erlotinib (Fidler *et al*, 2012). Objective response to monotherapy with IGF-1R monoclonal antibodies is rare, possibly due to expression of an aberrant form of the insulin receptor (IR), which may confer resistance to anticancer therapy and compensate for IGF-1R inhibition (Beliafore *et al*, 2009; Ulanet *et al*, 2010). Therefore, enhanced anti-tumor activity may be achieved by the co-inhibition of IGF-1R and IR (Buck *et al*, 2010; Janssen *et al*, 2014). Furthermore, in combination with an EGFR TKI, this co-inhibition may reduce the development of resistance due to the bidirectional cross-talk between the two receptors and the EGFR pathway (Gao *et al*, 2012; Fidler *et al*, 2012).

Linsitinib, an orally bioavailable, dual IGF-1R and IR inhibitor, has preclinical anti-proliferative effects in tumor cell lines and anti-tumor activity in IGF-1R xenograft models, including lung cancer (Ji *et al*, 2007; Mulvihill *et al*, 2009; McKinley *et al*, 2011; Zinn *et al*, 2013). Preliminary anti-tumor efficacy results observed for single-agent linsitinib in patients with solid tumors included partial responses in melanoma and adrenocortical carcinoma (Puzanov *et al*, 2015; Jones *et al*, 2015; Fassnacht *et al*, 2015). Furthermore, preclinical studies have shown linsitinib enhancement of erlotinib activity (Zhao *et al*, 2012), suggesting that linsitinib would be a promising agent for combination with EGFR inhibitors, especially in patients with NSCLC where cross-talk between the IGF-1R and EGFR pathways has been well-established (Pillai and Ramalingam SS, 2013; Fidler *et al*, 2012). A Phase I study of the linsitinib and erlotinib

combination, which included patients with NSCLC, illustrated a tolerable safety profile with no pharmacokinetic (PK) interaction between linsitinib and erlotinib (Macaulay *et al*, 2015).

We report the results of a Phase II study designed to compare the effect of maintenance linsitinib plus erlotinib vs erlotinib monotherapy on PFS in NSCLC patients with non-progression following four cycles of first-line platinum-based chemotherapy. Secondary efficacy endpoints included disease control rate (DCR), response upgrade rate (RUR), overall response rate (ORR), duration of response, and OS. Additionally, the safety profile as well as the PK of the linsitinib/erlotinib maintenance combination was evaluated.

Materials and Methods

Eligibility

Patients with histologically confirmed advanced NSCLC stages IIIB or IV with complete response (CR), partial response (PR), or stable disease (SD) following completion of first-line platinum based chemotherapy were eligible. Patients with disease progression at the time of study entry were not eligible. Testing for EGFR mutation status by either local or central testing was also required for study participation. Patients had an Eastern Cooperative Oncology Group status 0-1, a fasting glucose ≤150 mg/dL, and adequate hematopoietic, hepatic, and renal function. Patients with diabetes mellitus requiring insulinotropic or insulin therapy, a history of poorly controlled gastrointestinal disorders, or significant cardiovascular disease were excluded. Patients who had received prior IGF-1R therapy or concurrent maintenance bevacizumab were excluded.

The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice with the ethical principles of Helsinki and approved by the independent ethics committee or institutional review board for each site. Patients provided written consent prior to study initiation. The study is registered with ClinicalTrials.gov, NCT01186861.

Study design

Patients who met study criteria were randomized 1:1 to receive maintenance oral linsitinib 150 mg (recommended Phase II single agent dose [Puzanov *et al*, 2015]) or placebo BID on a continuous schedule combined with erlotinib 150 mg QD (approved single-agent dose), both starting on Day 1 and continuing for the entire treatment period (21 days). Patients were stratified by EGFR-activating mutation type (wild type vs exon 19 deletion/exon 21 L858R point mutation; non-activating mutations were grouped with wild type), tumor histology (squamous vs non-squamous), response to prior platinum-based chemotherapy (CR/PR vs SD), and smoking history (never vs former vs current). Dose modifications of either study drug could be made at the discretion of the investigator and were guided by the toxicity deemed most causally related to study treatment. Safety and efficacy data were reviewed by the data monitoring committee (DMC) at periodic intervals. Following recommendation of the DMC on April 23, 2013, all patients were unblinded because of lack of efficacy and discontinued from linsitinib or placebo. Patients remained on erlotinib and were followed for safety.

Efficacy and safety analysis

The primary efficacy endpoint, PFS, was defined as the time from randomization to disease progression based on Response Evaluation Criteria in Solid Tumors (RECIST) (v1.1) (Eisenhauer *et al*, 2009). Secondary efficacy endpoints included OS, defined as the time from

randomization to documented death; ORR, defined as proportion of patients with best overall response of CR or PR according to RECIST (v1.1); DCR, defined as proportion of patients with best overall response of CR, PR, or SD (with minimum duration of 6 weeks); RUR, defined as proportion of patients with a response upgrade in comparison to their best response at the start of the study. Additional secondary objectives included PFS according to EGFR mutation status and to squamous/non-squamous histology. Exploratory endpoints included expression of genes and proteins related to epithelial-to-mesenchymal transition (a potential biomarker of response to linsitinib), such as E-cadherin protein expression, as well as Kirsten rat sarcoma viral oncogene (KRAS) and phosphatidylinositol-4,5-bisphosphate 3-kinase and catalytic subunit alpha (PIK3CA) mutation status, and their relationship to clinical outcomes.

Blood and tissue samples were collected to assess PK, pharmacodynamic, and exploratory biomarkers. The PK analysis set included treated patients who had at least one blood sample with known time of sampling and dosing on the day of sampling. Plasma samples were used to measure concentrations of linsitinib and erlotinib. Pharmacodynamic and exploratory biomarker analyses consisted of the evaluation of proteins and nucleic acids in tumor samples or protein expression from tumor samples. KRAS and PIK3CA mutations were evaluated from plasma or tumor sample DNA. Tissue samples were also analyzed to determine E-cadherin protein expression (e.g., above median, below median, highest or lowest quartile) by means of immunohistochemistry (Quintiles, Westmont, IL). Plasma concentrations of IGF-1 were measured and compared predose in treatment periods 1 to 5.

The safety population included all patients who received at least one dose of treatment, and evaluation was based on adverse events (AEs), serious AEs (SAEs), clinical laboratory tests

(hematology and biochemistry), physical examination, vital signs, and electrocardiogram data. AEs and laboratory findings were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, v4.02.

Statistical analysis

Kaplan-Meier method was used to analyze the primary endpoint of PFS by treatment group. Hazard ratio (HR) of the treatment effect along with 95% confidence interval (CI) was calculated using a Cox proportional hazard model. The study was powered based on the secondary efficacy variable, OS. The sample size of *N*=200 (130 events) would yield 82% power to detect a 67% improvement, alpha=0.05. The study was to continue follow-up 5 months after the PFS primary analysis, which was powered (>99%, *n*=171 PFS events) to detect a 109% improvement in the linsitinib group compared with the placebo group using a two-sided log-rank test at a significance level of 0.05. The actual number of PFS events was 149, due to mandatory unblinding of the study prior to the pre-specified primary analysis of PFS. Patients who had not progressed at the time of analysis were censored at the date of last tumor assessment when non-progression was documented. PFS was also analyzed using log-rank stratified by EGFR mutation status and histology. OS was analyzed using the same statistical method as PFS, and patients still alive at the time of analysis were censored at the last alive date.

Response rates (DCR, RUR, and ORR) were analyzed using Fisher's exact test. PK analyses were summarized using descriptive statistics, as were demographic and other baseline characteristics. Analyses were performed using Statistical Analysis Software v9.1.

Results

Patients

The study was conducted at 80 sites in 9 countries including Brazil (15), Canada (7), Germany (13), Poland (6), Romania (7), Russia (8), South Korea (8), United Kingdom (7), and United States (9). Efficacy, disposition, and safety analyses were based on a July 2013 data cut off. A total of 205 patients were randomized, 102 to the linsitinib/erlotinib group and 103 to the placebo/erlotinib group, and were included in the final analysis set.

The safety analysis set comprised 201 patients who received at least one dose of study drug (100 in the linsitinib/erlotinib group and 101 in the placebo/erlotinib group). All 201 treated patients had at least one blood sample collected for PK analyses and made up the PK Analysis Set. After the start of treatment, 88 patients (86.3%) receiving linsitinib/erlotinib discontinued treatment compared with 81 (78.6%) receiving placebo/erlotinib. The majority of patients (74.6%) discontinued because of disease progression (71.6% linsitinib/erlotinib and 77.8% placebo/erlotinib). A similar proportion of patients in each group had AEs as the primary reason for discontinuation (11.4% linsitinib/erlotinib and 8.6% placebo/erlotinib). Other reasons for discontinuation included withdrawal of consent and medical/ethical reasons (6.8% and 1.1% linsitinib/erlotinib and 2.5% and 3.7% placebo/erlotinib, respectively).

The median duration of exposure to active comparison treatment was similar in the two treatment groups. In the linsitinib/erlotinib group, patients had a median duration of 104.5 days on linsitinib and 105 days on erlotinib. In the placebo/erlotinib group, the median duration was 105 days for both placebo and erlotinib. Baseline patient characteristics were balanced between the two groups (Table 1)**.** The median age was 61 years (range 36–83), and the majority of patients

were male (62.4%) and white (75.6%). The median time from initial diagnosis to randomization was 4.6 months, and the majority of patients had stage IV disease (92.2%) and adenocarcinoma histology (67.3%). A larger proportion of patients in the placebo group received prior radiation (22.3% placebo vs 15.7% linsitinib), and best response prior to locally advanced or metastatic treatment was fairly even in the two treatment groups with PR = 24.8% vs 29.1% and SD = 71.6% vs 68.9% in the linsitinib/erlotinib group vs placebo/erlotinib group, respectively.

Efficacy

DMC reviewed safety and efficacy data at predefined enrollment and event intervals throughout the study. Following a DMC analysis that showed no difference to demonstrate superiority in the linsitinib/erlotinib vs the placebo/erlotinib group, the study was terminated and unblinded prior to the pre-specified PFS analysis. No statistically significant difference was found between the two treatment groups in PFS. Median PFS (linsitinib/erlotinib vs placebo/erlotinib) was 125 vs 129 days (P=0.601) (Table 2, Figure 1A). Additionally, subgroup analyses of the full analysis set (patients with at least one dose of linsitinib) showed no PFS differences between the two treatment groups based on mutation status, gender, age, histology, response to prior chemotherapy, or smoking history, of which the treatment arms were well balanced (Table 3). Furthermore, there was no difference between the two treatment groups in the secondary OS analyses (Table 2, Figure 1B). The objective response rate was 15.7% for the linsitinib group vs 11.7% for the placebo group. One patient treated with linsitinib/erlotinib achieved CR and 15 achieved PR compared with 12 patients with PR who received placebo/erlotinib and no achievement of CR (Table 2).

Median linsitinib plasma concentrations at pre-dose and 4 hours in all treatment periods (TPs) are listed in Table 4. Pre-dose concentrations of erlotinib at steady state (TP2 and TP3) were similar in both patients treated with linsitinib/erlotinib and placebo/erlotinib, suggesting a lack of drug-drug interaction between linsitinib and erlotinib.

An increase in plasma IGF-1 concentration is an indirect measure of IGF-1R signaling inhibition. The median plasma concentrations of IGF-1 remained similar from TP1 to TP3 in patients treated with placebo/erlotinib (Table 4). In patients treated with linsitinib/erlotinib, the median pre-dose plasma IGF-1 concentrations increased from 40 ng/mL inTP1 to 65 ng/mL in TP4, suggesting a pharmacodynamic effect.

With respect to analysis of tissue biomarkers that may have influenced efficacy, there were 90 patients treated with linsitinib/erlotinib and 92 patients treated with placebo/erlotinib with biomarker data (Table 3). Activating KRAS mutations were observed in 16 patients in each treatment group. Activating PIK3CA mutations were observed in one patient treated with linsitinib/erlotinib and four patients treated with placebo/erlotinib. Activating EGFR mutations were observed in 22 patients treated with linsitinib/erlotinib and 19 patients treated with placebo/erlotinib. The small number of patients with KRAS, PIK3CA, and/or EGFR mutations precluded a detailed analysis of these parameters with respect to the relationship of mutation status to patient's outcomes. E-cadherin levels were measured in 78 patients. E-cadherin H-scores were within the normal range for the majority of patients and were low (<100) in three patients treated with linsitinib/erlotinib and six patients treated with placebo/erlotinib. The only significant difference in PFS was noted for a small subgroup of patients with both EGFR wild type and E-cadherin lower than the median, favoring the linsitinib group with median PFS

linsitinib/erlotinib (*n*=28) vs placebo/erlotinib (*n*=31) of 128 vs 82 days and HR 0.52 (0.29–0.94) (Table 3).

Safety

Treatment emergent AEs (TEAEs) were similar in both treatment groups. The most common TEAEs (occurring in ≥20% of patients in either group) were rash/drug eruption (67.0% for linsitinib/erlotinib vs 58.4% for placebo/erlotinib), diarrhea (44.0% vs 32.7%), decreased appetite (30.0% vs 20.8%), and nausea (22.0% vs 18.8%), respectively. Grade 3/4 TEAEs of rash/drug eruption (8.0%) and diarrhea (5.0%) occurred in ≥5% of patients treated with linsitinib/erlotinib. There were no Grade 3/4 TEAEs in ≥5% of patients in patients treated with placebo/erlotinib.

Treatment-related AEs were more frequent in patients treated with linsitinib/erlotinib (93% vs 87.1% for placebo/erlotinib). The most common treatment-related AEs in patients receiving linsitinib/erlotinib or placebo/erlotinib, respectively, were drug rash/eruption (67.0% vs 58.4%) and diarrhea (38.0% vs 28.7%) (Table 5). A higher proportion of patients receiving linsitinib/erlotinib had treatment-related serious AEs (15% vs 7.9% placebo/erlotinib). The incidence of TEAEs that led to permanent discontinuation of study drug was also higher in patients treated with linsitinib/erlotinib (15%) than with placebo/erlotinib (10.9%). Of these, eight patients in the linsitinib/erlotinib group and three patients in the placebo/erlotinib group discontinued study medication due to a treatment-related AE. Similarly, serious TEAEs and serious treatment-related AEs were more common in patients treated with linsitinib/erlotinib. Serious TEAEs were reported for 36 (36.0%) patients in the linsitinib/erlotinib group and 29

(28.7%) patients in the placebo/erlotinib group. Serious treatment-related AEs were reported in 15 (15.0%) patients receiving linsitinib/erlotinib and 8 (7.9%) placebo/erlotinib.

AEs of special interest, including renal, hepatic, cardiac, glycemic, and neurologic AEs, were also investigated. Overall, six (6.0%) patients receiving linsitinib/erlotinib and eight (7.9%) placebo/erlotinib experienced renal and urinary disorders. In addition, 11 (11.0%) patients who received linsitinib/erlotinib and ten (9.9%) patients who received placebo/erlotinib experienced increased blood creatinine and two (2.0%) patients who received linsitinib/erlotinib and one (1.0%) patient who received placebo/erlotinib experienced hepatobiliary disorders. Most increases in liver enzymes and liver toxicity markers were low-grade for both treatment groups. Cardiac disorders (including QTcF interval prolongation) occurred in five (5.0%) patients, each receiving either linsitinib/erlotinib or placebo/erlotinib. Serious cardiac TEAEs occurred in two (2%) patients receiving placebo/erlotinib, but not in patients receiving linsitinib/erlotinib. Hyperglycemia occurred in 19 (19.0%) patients receiving linsitinib/erlotinib compared with eight (7.9%) patients receiving placebo/erlotinib; the events were treatment-related in 15 (15.0%) patients receiving linsitinib/erlotinib (4.0% Grade 3/4) and four (4.0%) patients receiving placebo/erlotinib (all grade 1 or 2). Nervous system disorders were experienced in 20.0% and 28.7% of patients receiving linsitinib/erlotinib and placebo/erlotinib, respectively. Overall, five patients had nervous system TEAEs considered serious: one (1.0%) patient receiving linsitinib/erlotinib and four (4.0%) patients receiving placebo/erlotinib.

There were 12 deaths that occurred during the study, none of which were related to study treatment. In patients who received linsitinib/erlotinib, 1 patient died on Day 7 of study treatment due to bacterial pneumonia and six patients died within 30 days of last dose. In patients who

received placebo/erlotinib, five patients died within 30 days of last dose. The causes of death in the patients who received linsitinib/erlotinib were respiratory failure or distress (2), pneumonia, dyspnea, pulmonary embolism, abdominal sepsis, and disease progression; and in the patients receiving placebo/erlotinib the causes were disease progression (2), dyspnea, respiratory failure, and neurological decompensation.

Discussion

This randomized Phase II study investigated the effect of linsitinib maintenance therapy in combination with erlotinib compared with erlotinib alone (plus placebo) as maintenance therapy in patients with NSCLC who had not progressed following four cycles of platinum-based chemotherapy. The study confirmed an acceptable safety profile for the combination of linsitinib and erlotinib; however, linsitinib did not improve PFS, OS, or ORR compared with erlotinib monotherapy.

The safety profile in both treatment groups was consistent with expectations for patients with advanced stage NSCLC treated with EGFR inhibitors (Passaro *et al*, 2014), or linsitinib (Puzanov *et al*, 2015; Jones *et al*, 2015; Fassnacht *et al*, 2015). TEAEs were similar in both treatment groups, although SAEs, treatment-related AEs, and serious treatment-related AEs were more frequent among patients randomized to the linsitinib group, as were treatment discontinuations. As expected, due to linsitinib's mechanisms of action, there was an increased incidence of hyperglycemia in patients who received linsitinib, although none of the incidents were considered serious.

Prior clinical studies have demonstrated that maintenance therapy using erlotinib alone in NSCLC is generally well tolerated with a modest prolongation of PFS in patients unselected for presence of sensitizing EGFR mutation (Cappuzzo *et al*, 2010; Perol *et al*, 2012). The addition of erlotinib to bevacizumab in maintenance was shown to improve PFS but not OS in a Phase III randomized study (Johnson *et al*, 2013). Although generally well tolerated, the lack of survival benefit and increased toxicity associated with the addition of erlotinib to bevacizumab maintenance did not lead to a new maintenance standard of care. The rationale for combining linsitinib and erlotinib in maintenance was based on preclinical studies that demonstrated the reciprocal, compensatory signaling between EGFR and IGF-1R pathways on inhibition of either pathway (Buck *et al*, 2008). Synergistic effects on cancer cell and tumor growth using combinations of linsitinib or other IGF-1R targeted agents with erlotinib were observed in preclinical studies (Buck *et al*, 2008). Further studies have also suggested a role for IGF-1R in mediating resistance to EGFR-targeted therapies (Guix *et al*, 2008; Stewart *et al*, 2015). Despite strong preclinical evidence and early clinical studies, the results of the present study do not demonstrate any additional benefit from the combination of linsitinib with erlotinib. The results for PFS on both treatment arms are consistent with those obtained for previous studies of maintenance therapy with erlotinib alone (Cappuzzo *et al*, 2010) or with chemotherapy (Paz-Ares *et al*, 2013).

PK data in this study indicated that pre-dose concentrations of erlotinib were similar in both treatment groups and results were consistent with the Phase 1 study, indicating a lack of substantial PK drug-drug interaction between erlotinib and linsitinib (Macaulay *et al*, 2015). Moreover, linsitinib concentrations were similar to those in single-agent studies. Detection of increased plasma IGF-1, a putative pharmacodynamic biomarker of IGF-1R inhibition, in

patients who received linsitinib, provides evidence that the dose administered was sufficient to modulate the IGF-1R pathway in these patients (Puzanov *et al*, 2015; Jones *et al*, 2015). Therefore, the negative result of this study cannot be attributed to inadequate dosing of either erlotinib or linsitinib. Although there is a theoretical, scientific rationale for dual inhibition of IGF-1R/EGFR (Scagliotti and Novello, 2012), several studies have now reported no improvement in PFS or OS for dual IGF-1R and EGFR inhibition (Weickhardt *et al*, 2012; Ramalingam *et al*; 2011 Scagliotti *et al*, 2015). IGF-1R signaling is inherently complex, involving cross-talk interactions with various feedback, and compensatory and redundant signaling pathways in cancer cells (Jin *et al*, 2013). A deeper understanding of the interactions between these pathways is necessary before further development of this combination strategy in NSCLC is warranted.

Biomarker subgroup treatment may be an important caveat in NSCLC maintenance treatment (Mery *et al*, 2015; Zhou *et al*, 2015; Gerber and Schiller, 2013). In the context of maintenance erlotinib, in the SATURN trial the PFS was 44 weeks for the subgroup of patients with tumors bearing activating EGFR mutations compared with 14 weeks for patients without mutation (Cappuzzo *et al*, 2010). In the current study, patients with activating EGFR mutations had substantially longer survival on both treatment arms (651 days on the placebo arm and 463 days on the linsitinib arm). There was no significant difference between the arms for this subgroup, but the survival results observed likely reflect the greater efficacy of erlotinib for tumors with activating EGFR mutation and reinforce that future trials should consider this population separately from the wild type population when considering sample size and statistical assumptions. The number of patients in this subgroup is unfortunately too low to determine any

signal of benefit from the addition of linsitinib, which in theory could mitigate EGFR-TKI resistance due to IGF-1R activation.

Uniform treatment across subgroups, including those defined by biomarker differences, may be an important caveat in the treatment of advanced NSCLC (Mery *et al*, 2015) and, more specifically, for maintenance treatment (Zhou *et al*, 2015; Gerber and Schiller, 2013). A difference in PFS was observed in patients with both EGFR wild type and E-cadherin lower than the median, favoring the linsitinib group with median PFS linsitinib vs placebo of 128 vs 82 days (HR=0.52, 95% CI 0.29–0.94). Other numeric differences in PFS that did not reach statistical significance were observed for patients aged ≥65 years in whom PFS was shorter for the linsitinib treatment arm (127 vs 171 days; HR=1.30, 95% CI 0.72–2.34). Additionally, the PFS was longer in the linsitinib/erlotinib treatment arm among patients who were former or current smokers, whereas the PFS for patients who had never smoked was longer on the placebo/erlotinib arm. This is consistent with the result for patients with activating EGFR mutation, which is likely to occur more frequently in the never-smokers. Similarly, never-smoking and EGFR mutation are known to associate with adenocarcinoma biology (Zhou *et al*, 2015; Gerber and Schiller, 2013). In the current study, patients with squamous tumor histology had a median PFS of 127 days vs 113 days (HR=0.67, 95% CI 0.36–1.24) on linsitinib and placebo, respectively. Finally, although numerically a very small subset (*n*=16 for each arm), the PFS for patients with K-RAS mutated positive tumors on linsitinib/erlotinib was superior to that for placebo/erlotinib treatment (128 vs 87 days; HR=0.61, 95% CI 0.28–1.36). Looking at all the subset data together, there is a trend for linsitinib to numerically improve the results over erlotinib alone in patient subgroups where EGFR-TKI are generally less active, such as squamous cell histology, former or current smokers, and EGFR wild type (with an emphasis on

patients with a low E-cadherin level), and in patients with K-RAS mutant tumors. At the present time, these data are an insufficient basis for further clinical evaluation of linsitinib/erlotinib in patients with these characteristics but are provocative for further preclinical evaluation of relevant tumor types and molecular contexts to explore for this therapeutic approach.

Overall, linsitinib maintenance therapy in combination with erlotinib did not show an improvement of PFS or OS compared with erlotinib alone in molecularly unselected non-progressing NSCLC patients who had completed first-line platinum combination chemotherapy and does not support further investigation of this combination as maintenance for advanced NSCLC. The negative results cannot be attributed to inadequate drug dosing or excessive toxicity requiring dose adjustments or withdrawal. The results emphasize the need for development of mechanism-based therapies in clinical populations characterized for relevant pharmacodynamic and predictive biomarkers. Identification of candidate biomarkers for response to IGF-1R targeted therapies is required for further clinical development of this strategy.

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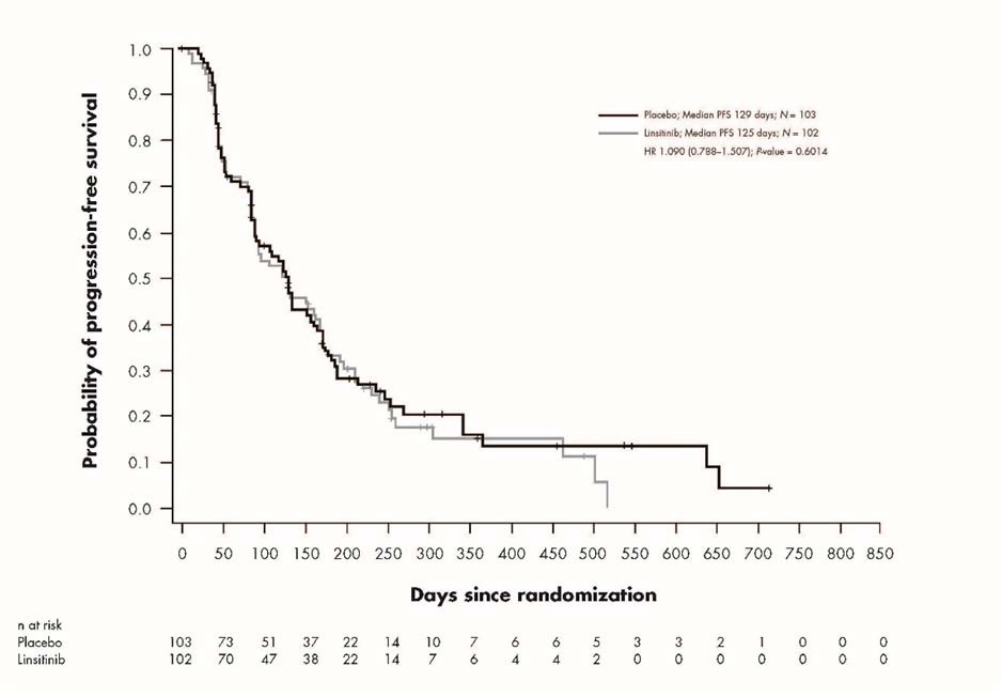
Titles and legends to figures

Figure 1. Progression-free survival (A) and overall survival (B), full analysis set.

CI=confidence interval; HR=hazard ratio

Figure 1

(A)


Probability of progression-free survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Placebo; Median PFS 129 days; N = 103
Linsitinib; Median PFS 125 days; N = 102
HR 1.090 (0.788–1.507); P-value = 0.6014
0 50 100 150 200 250 300 350 400 450 500 550 600 650 700 750 800 850
Days since randomization
n at risk
Placebo 103 73 51 37 22 14 10 7 6 6 5 3 3 2 1 0 0 0
Linsitinib 102 70 47 38 22 14 7 6 4 4 2 0 0 0 0 0 0 0

(B)

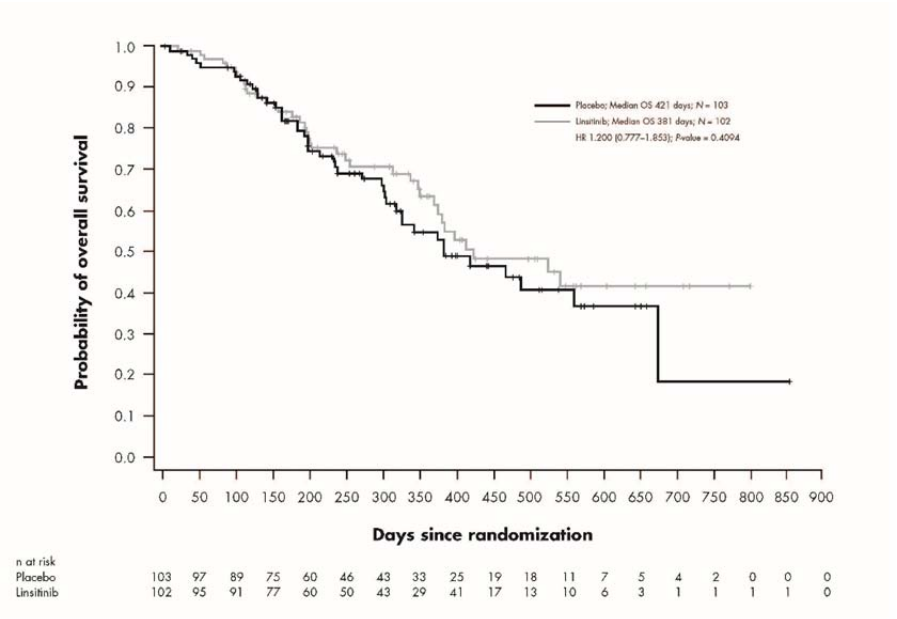

Probability of overall survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Placebo; Median OS 421 days; N = 103
Linsitinib; Median OS 381 days; N = 102
HR 1.200 (0.777–1.853); P-value = 0.4094
0 50 100 150 200 250 300 350 400 450 500 550 600 650 700 750 800 850 900
Days since randomization
n at risk
Placebo 103 97 89 75 60 46 43 33 25 19 18 11 7 5 4 2 0 0 0
Linsitinib 102 95 91 77 60 50 43 29 41 17 13 10 6 3 1 1 1 1 0

Table 1. Baseline patient characteristics			
	Linsitinib/Erlotinib (n=102)	Placebo/Erlotinib (n=103)	Total (n=205)
Age			
Median (range)	62.0 (36–81)	60.0 (40–83)	61.0 (36–83)
Sex, n (%)			
Male	62 (60.8)	66 (64.1)	128 (62.4)
Female	40 (39.2)	37 (35.9)	77 (37.6)
Race, n (%)			
White	78 (76.5)	77 (74.8)	155 (75.6)
Black	4 (3.9)	1 (1.0)	5 (2.4)
Asian	17 (16.7)	24 (23.3)	41 (20.0)
Other	3 (2.9)	1(1.0)	4 (2.0)
ECOG performance score, n (%)			
0	36 (35.3)	32 (31.1)	68 (33.2)
1	66 (64.7)	71 (68.9)	137 (66.8)
Cigarette smoking history, n (%)			
Former smoker	59 (57.8)	60 (58.3)	119 (58.0)
Never smoked	20 (19.6)	20 (19.4)	40 (19.5)
Current smoker	23 (22.5)	23 (22.3)	46 (22.4)
NSCLC stage, n (%)			
Stage IIIB	7 (6.9)	9 (8.7)	16 (7.8)
Stage IV	95 (93.1)	94 (91.3)	189 (92.2)
Histological subtype, n (%)			
Adenocarcinoma	69 (67.6)	69 (67.0)	138 (67.3)
Squamous cell carcinoma	20 (19.6)	24 (23.3)	44 (21.5)
Undifferentiated large cell carcinoma	2 (2.0)	1 (1.0)	3 (1.5)
Mixed histology	7 (6.9)	6 (5.8)	13 (6.3)
Other	4 (3.9)	3 (2.9)	7 (3.4)
Time from initial diagnosis, months			
Mean (SD)	7.2 (12.33)	6.7 (8.48)	6.9 (10.55)
Median (range)	4.7 (4-117)	4.5 (3-67)	4.6 (3-117)
Prior Treatment			
Prior radiation therapy, *n* (%)	16 (15.7)	23 (22.3)	39 (19.0)
Prior disease-related surgery, *n* (%)	30 (29.4)	33 (32.0)	63 (30.7)
Prior regimen treatment, *n* (%)			
All	102 (100)	103 (100)	205 (100)
Neo-adjuvant	0 (0)	0 (0)	0 (0)
Adjuvant	0 (0)	1 (1.0)	1 (0.5)
Abbreviations: ECOG=Eastern Cooperative Oncology Group; LDH=lactate dehydrogenase; NSCLC=non–small cell lung cancer; SD=standard deviation; ULN=upper limit of normal.			

Table 2. Summary of efficacy				
Efficacy Endpoint	Linsitinib/Erlotinib (n=102)	Placebo/Erlotinib (n=103)	HR (95% CI)	P-value
Progression-free survival				
Number of events, *n* (%)	74 (72.5)	75 (72.8)	1.09	0.601
Median, days (95% CI)	125 (88, 167)	129 (88, 158)	(0.788, 1.507)	
Overall survival				
Number of events, *n* (%)	44 (43.1)	38 (36.9)	1.2	0.409
Median, days (95% CI)	381 (316, 672)	421 (367, NR)	(0.777, 1.853)	
Best overall response, n (%)				
Complete response	1 (1.0)	0 (0)	NA	NA
Partial response	15 (14.7)	12 (11.7)		
Stable disease	53 (52.0)	58 (56.3)		
Progressive disease	27 (26.5)	26 (25.2)		
Not evaluated	6 (5.9)	7 (6.8)		
Disease control rate[a]				
n (%)	69 (67.7)	70 (68.0)	NA	NA
95% CI	(57.66, 76.58)	(58.04, 76.82)		
Objective response rate[b]				
n (%)	16 (15.7)	12 (11.7)	NA	NA
95% CI	(9.24, 24.22)	(6.17, 19.47)		
Response upgrade rate[c]				
n (%)	11 (10.78)	9 (8.74)	NA	NA
95% CI	(5.51, 18.48)	(4.07, 15.94)		

Abbreviations: CI=confidence interval; HR=hazard ratio; NA=not applicable.

[a]Disease control rate = complete response + partial response + stable disease.

[b]Overall response rate = complete response + partial response.

[c]Response upgrade rate = proportion of patients with a response upgrade in comparison to their best response at the start of the study.

Table 3. Subgroup analysis and biomarker subgroup analysis of PFS							
	Linsitinib/Erlotinib (n=102)			Placebo/Erlotinib (n=103)			HR, linsitinib vs placebo (95% CI)
	N	Events *n* , (%)	Median in days	N	Events *n* , (%)	Median in days	
Subgroup analysis[a]							
EGFR mutation status							
Wild type	85	67 (78.8)	92	85	70 (82.4)	106	1.10 (0.78–1.54)
Activating	17	7 (41.2)	463	18	5 (27.8)	651	1.81 (0.52–6.32)
Histology							
Squamous	23	19 (82.6)	127	26	25 (96.2)	113	0.67 (0.36–1.24)
Non-squamous	79	55 (69.6)	125	77	50 (64.9)	133	1.26 (0.86–1.86)
Response to prior platinum-based therapy							
Complete/partial response	28	23 (82.1)	85	29	22 (75.9)	133	1.32 (0.73–2.40)
Stable disease	74	51 (68.9)	154	74	53 (71.6)	127	1.02 (0.70–1.51)
Cigarette smoking history							
Never	20	13 (65.0)	92	20	13 (65.0)	171	1.56 (0.71–3.43)
Former	59	41 (69.5)	121	60	46 (76.7)	116	0.91 (0.60–1.39)
Current	23	20 (87.0)	151	23	16 (69.6)	106	0.97 (0.50–1.91)
Cotinine							
Positive	22	17 (77.3)	125	21	17 (81.0)	119	1.02 (0.51–2.03)
Negative	72	51 (70.8)	121	80	57 (71.3)	129	1.07 (0.73–1.57)
Sex							
Male	62	47 (75.8)	131	66	49 (74.2)	116	1.07 (0.71–1.60)
Female	40	27 (67.5)	95	37	26 (70.3)	133	1.18 (0.69–2.03)
Age group (years)							
<65	57	45 (78.9)	121	72	57 (79.2)	109	1.03 (0.69–1.52)
≥65	45	29 (64.4)	127	31	18 (58.1)	171	1.30 (0.72–2.34)
Biomarker subgroup analysis[b]							
KRAS mutation status							
Wild type	72	50 (69.4)	160	74	54 (73.0)	133	1.01 (0.69–1.49)
Activating	16	13 (81.3)	128	16	14 (87.5)	87	0.61 (0.28–1.36)
PIK3CA mutation status							
Wild type	87	61 (70.1)	154	84	64 (76.2)	124	0.89 (0.63–1.27)
Activating	1	1 (100)	131	4	2 (50.0)	ND	3.46 (0.22–55.8)
EGFR mutation status							
Wild type	68	53 (77.9)	121	73	60 (82.2)	106	1.01 (0.70–1.47)
Activating	22	11 (50.0)	304	19	9 (47.4)	340	1.28 (0.51–3.20)
E-cadherin in EGFR wild type							
≥Median	30	25 (83.3)	83	33	27 (81.8)	133	1.60 (0.92–2.78)
<Median	28	20 (71.4)	128	31	26 (83.9)	82	0.52 (0.29–0.94)

Abbreviations: EGFR=epidermal growth factor receptor; HR=hazard ratio.

[a]Subgroup analysis of the full analysis set, which includes any patient who received at least 1 dose of linsitinib.

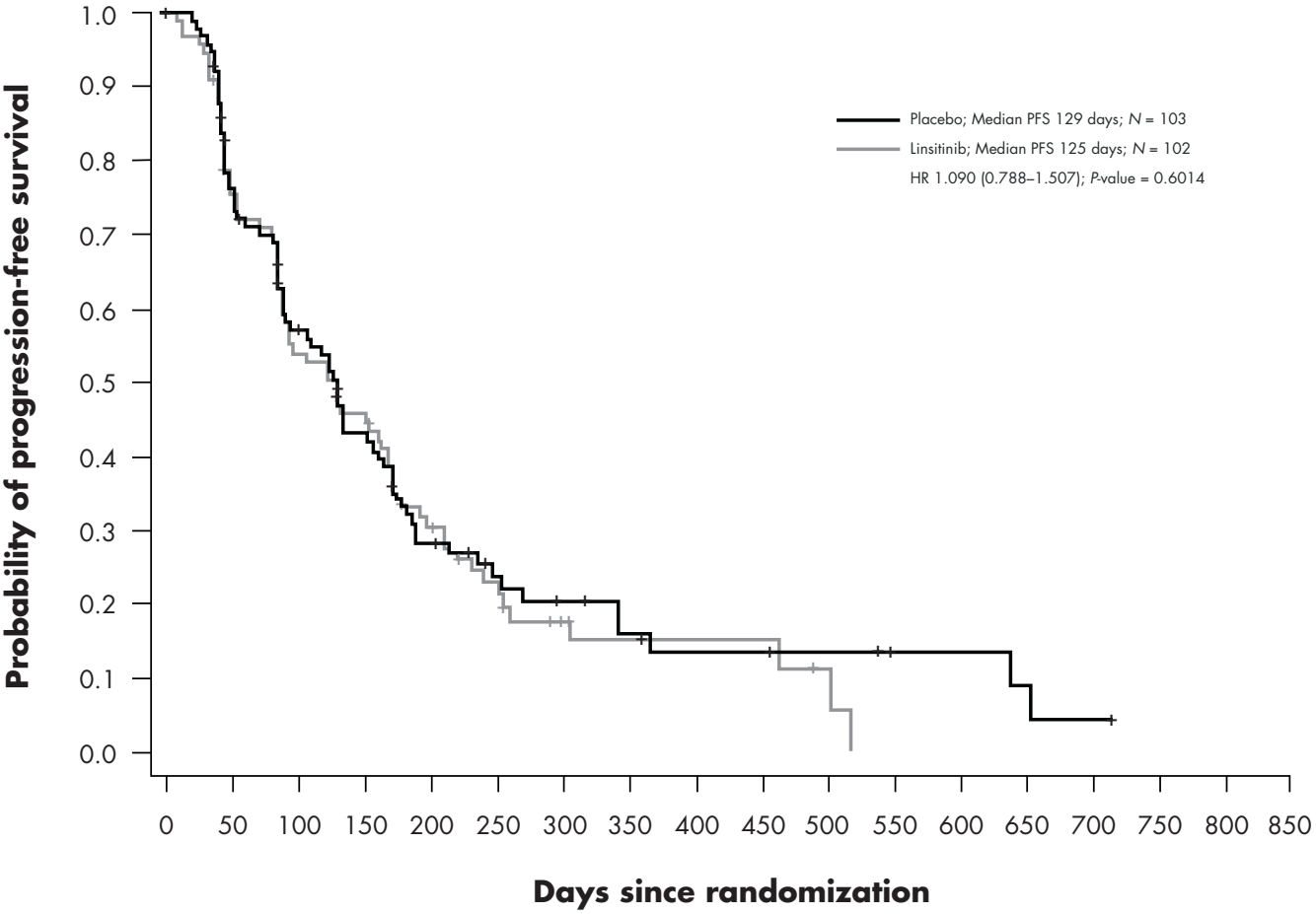
[b]Biomarker subgroup analysis of patients who had sufficient tissue/plasma samples for analysis among similar evaluable patients.

Table 4. Pharmacokinetics of erlotinib and linsitinib and pharmacodynamics of insulin-like growth factor-1								
	Linsitinib/erlotinib				Placebo/erlotinib			
	n	Predose	*n*	4-hr postdose	*n*	Predose	*n*	4-hr postdose
TP1, Day 1	67	0 (0–1380)	31	816 (0–3700)	64	0 (0–84)	36	883 (0–2740)
TP2, Day 1	64	974 (0–3370)	25	1160 (0–10300)	68	1045 (0–3360)	26	1565 (195–3260)
TP3, Day 1	58	930 (0–3380)	13	1100 (0–2660)	65	1210 (3–3810)	15	1100 (1.4–5290)
Plasma concentration of linsitinib; median, ng/ml (range)								
TP1, Day 1	77	0	21	1030 (0–2620)	NA	NA	NA	NA
TP2, Day 1	69	455 (0–2970)	21	898 (18–3190)	NA	NA	NA	NA
TP3, Day 1	54	639 (0–2850)	17	1250 (42–3210)	NA	NA	NA	NA
Predose plasma concentrations of insulin-like growth factor-1; median, ng/ml (range)								
TP1, Day 1	93	40 (13–122)			93	46 (14–128)		
TP2, Day 1	86	61 (11–207)			84	47 (1–132)		
TP3, Day 1	65	62 (20–198)			72	45 (12–119)		
TP4, Day 1	54	65 (20–147)			57	39 (17–113)		
TP5, Day 1	50	63 (5–188)			49	44 (14–130)		
Abbreviations: NA=not applicable; TP=treatment period.								

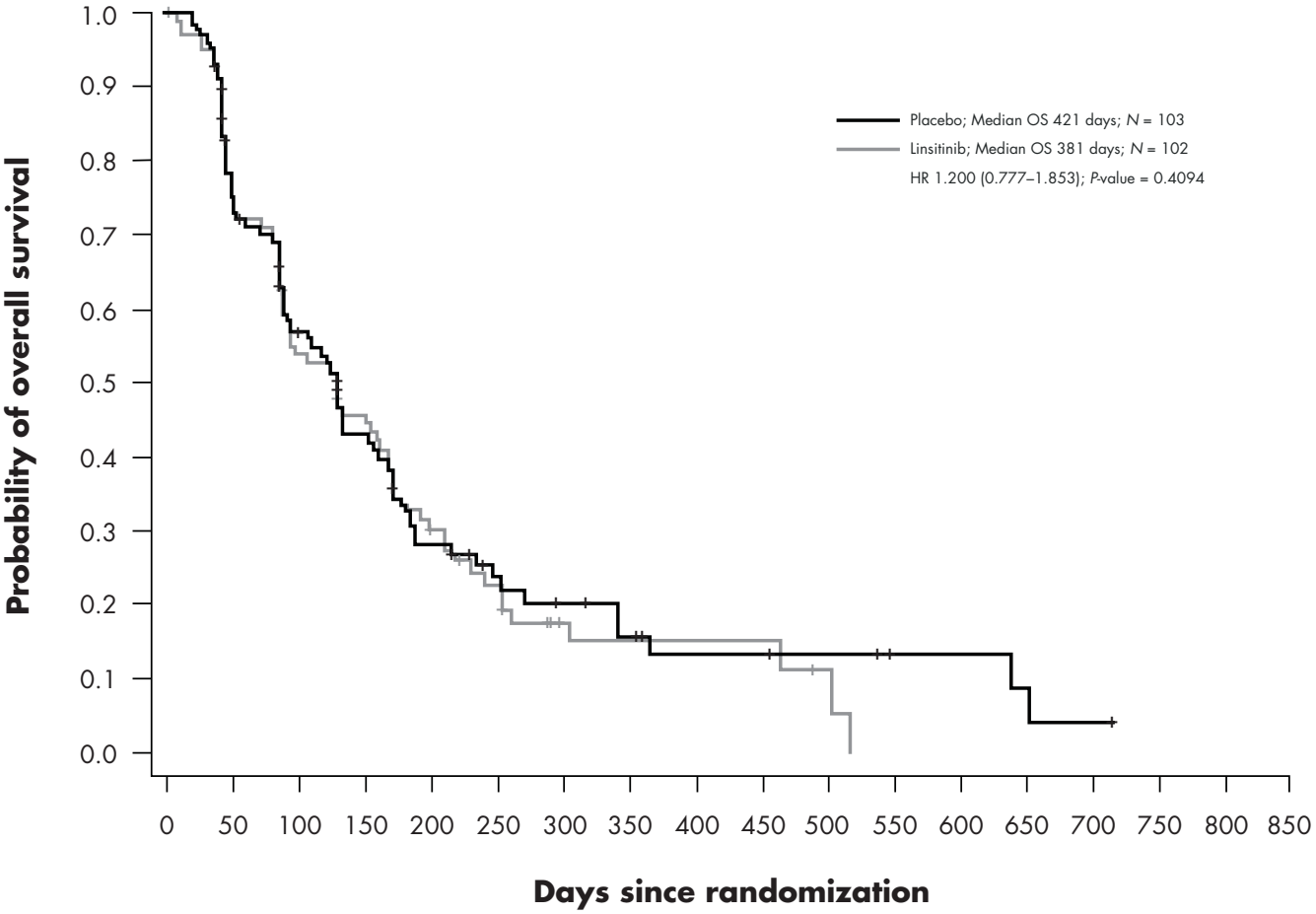
Table 5. All-grade treatment-related AEs ≥10% patients in either treatment and grade 3/4 treatment-related Aes

	Linsitinib/Erlotinib (n=100)		Placebo/Erlotinib (n=101)		Total (N=201)	
Adverse Event, *n* (%)	**All grade**	**Grade 3/4**	**All grade**	**Grade 3/4**	**All grade**	**Grade 3/4**
Drug eruption	67 (67.0)	8 (8.0)	59 (58.4)	4 (4.0)	126 (62.7)	12 (6.0)
Diarrhea	38 (38.0)	4 (4.0)	29 (28.7)	2 (2.0)	67 (33.3)	6 (3.0)
Decreased appetite	20 (20.0)	0 (0)	15 (14.9)	0 (0)	35 (17.4)	0 (0)
Pruritus	14 (14.0)	0 (0)	19 (18.8)	0 (0)	33 (16.4)	0 (0)
Nausea	18 (18.0)	2 (2.0)	11 (10.9)	0 (0)	29 (14.4)	2 (1.0)
Dry skin	12 (12.0)	2 (2.0)	10 (9.9)	0 (0)	22 (10.9)	2 (1.0)
Fatigue	11 (11.0)	2 (2.0)	10 (9.9)	2 (2.0)	21 (10.4)	4 (2.0)
Paronychia	9 (9.0)	0 (0)	11 (10.9)	2 (2.0)	20 (10.0)	2 (1.0)
Vomiting	13 (13.0)	1 (1.0)	7 (6.9)	1 (1.0)	20 (10.0)	2 (1.0)
Hyperglycemia	15 (15.0)	4 (4.0)	4 (4.0)	0 (0)	19 (9.5)	4 (2.0)
Increased ALT	12 (12.0)	4 (4.0)	5 (5.0)	2 (2.0)	17 (8.5)	6 (3.0)
Stomatitis	11 (11.0)	1 (1.0)	6 (5.9)	1 (1.0)	17 (8.5)	2 (1.0)
Increased AST	7 (7.0)	0 (0)	6 (5.9)	2 (2.0)	13 (6.5)	2 (1.0)

Abbreviations: AE=adverse event; ALT=alanine transferase; AST=aspartate transferase.



n at risk																		
Placebo	103	73	51	37	22	14	10	7	6	6	5	3	3	2	1	0	0	0
Linsitinib	102	70	47	38	22	14	7	6	4	4	2	0	0	0	0	0	0	0



n at risk																		
Placebo	103	73	51	37	22	14	10	7	6	6	5	3	3	2	1	0	0	0
Linsitinib	102	70	47	38	22	14	7	6	4	4	2	0	0	0	0	0	0	0