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Randomised 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

Tudor-Eliade Ciuleanu*[,1], Samreen Ahmed[2], Joo-Hang Kim[3], Jörg Mezger[4], Keunchil Park[5], Michael Thomas[6], Jihong Chen[7,9], Srinivasu Poondru[7], Jan M VanTornout[7,9], Debbie Whitcomb[7] and Fiona Blackhall[8]

[1]Oncological Institute I Chiricuta and UMF Iuliu Hatieganu, Cluj-Napoca, Romania; [2]Leicester Royal Infirmary, Leicester, UK; [3]CHA Bundang Medical Center, CHA University, Gyeonggi-do, Korea; [4]Saint Vincentius-Kliniken Karlsruhe, Karlsruhe, Germany; [5]Samsung Medical Center Sungkyunkwan University School of Medicine, Seoul, Korea; [6]Translational Lung Research Center Heidelberg (TLRC-H), Member of the German Center for Lung Research (DZL), Heidelberg, Germany; [7]Astellas Pharma Global Development, Northbrook, IL, USA and [8]Manchester University and The Christie Hospital NHS Foundation Trust, Manchester, UK

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

Methods: In this Phase II randomised trial, patients without progression following four cycles of first-line platinum-based chemotherapy ($N = 205$) 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.

*Correspondence: Dr T-E Ciuleanu; E-mail: Tudor_ciuleanu@hotmail.com
[9]Formerly with Astellas Pharma Global Development at the time of this study.

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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, most 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 harbour targetable mutations typically consists of 4–6 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 approach) (Genestreti *et al*, 2015; Zhang *et al*, 2015). Agents used in continuation maintenance chemotherapy include pemetrexed (Paz-Ares *et al*, 2013), bevacizumab (Sandler and Herbst, 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 *et al*, 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). However, the extent of improvement varies with the type of maintenance therapy and the patient population (Lu *et al*, 2015; Zhang *et al*, 2015; Zhou *et al*, 2015).

Erlotinib, an EGFR-TKI used for first-line therapy in patients with NSCLC with sensitising mutations (Melosky, 2014), has demonstrated statistically significant, although 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 randomised, Phase III clinical trial (Cappuzzo *et al*, 2010). However, in most patients, erlotinib resistance is an eventual occurrence, either from primary resistance or as acquired resistance via secondary *EGFR* mutations (e.g., 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, 2016).

The insulin-like growth factor 1 (IGF-1) signalling pathway is involved in tumour cell proliferation, survival, and invasiveness, and shares downstream signalling 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 tumourigenesis. IGF-1R is aberrantly expressed in tumours, and its overexpression is associated with decreased survival in several tumour types, including NSCLC (Pollack, 2012; Kim *et al*, 2014; King *et al*, 2014). Furthermore, acquired resistance to reversible EGFR-TKIs has been reported in NSCLC cells engaging this pathway, whereas an IGF1-R inhibitor combined 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 such as 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-tumour activity may be achieved by co-inhibition of IGF-1R and IR (Buck *et al*, 2010; Janssen and Varewijck, 2014). Furthermore, when combined 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 (Fidler *et al*, 2012; Gao *et al*, 2012).

Linsitinib, an orally bioavailable, dual IGF-1R and IR inhibitor, has preclinical anti-proliferative effects in tumour cell lines and anti-tumour 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-tumour efficacy results were observed for single-agent linsitinib in patients with solid tumours, including partial responses in patients with melanoma and adrenocortical carcinoma (Fassnacht *et al*, 2015; Jones *et al*, 2015; Puzanov *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 in whom cross-talk between the IGF-1R and EGFR pathways has been well established (Fidler *et al*, 2012; Pillai and Ramalingam, 2013). A Phase I study of 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*, 2016).

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 patients with NSCLC 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 and the PK of the linsitinib/erlotinib maintenance combination were 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 performance status 0–1, a fasting glucose $\leqslant$150 mg/dL, and adequate haematopoietic, 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 randomised 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 (TP; 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), tumour 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 23 April 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 randomisation 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 randomisation to documented death; ORR, defined as the proportion of patients with best overall response of CR or PR according to RECIST 1.1; DCR, defined as the proportion of patients with best overall response of CR, PR, or SD (with minimum duration of 6 weeks); RUR, defined as the 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 tumour samples or protein expression from tumour samples. *KRAS* and *PIK3CA* mutations were evaluated from plasma or tumour sample DNA. Tissue samples were also analysed to determine E-cadherin protein expression (e.g., above median, below median, and highest or lowest quartile) by means of immunohistochemistry (Quintiles, Westmont, IL, USA). Plasma concentrations of IGF-1 were measured and compared predose in TPs 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 (haematology and biochemistry), physical examination, vital signs, and electrocardiogram data. Adverse events 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 analyse 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 tumour assessment when non-progression was documented. PFS was also analysed using log-rank stratified by *EGFR* mutation status and histology. OS was analysed 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 analysed using Fisher's exact test. PK analyses were summarised 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 nine countries including Brazil (15), Canada (7), Germany (13), Poland (6), Romania (7), Russia (8), South Korea (8), the United Kingdom (7), and the United States (9). Efficacy, disposition, and safety analyses were based on a July 2013 data cut-off. A total of 205 patients were randomised, 102 to the linsitinib/erlotinib group and 103 to the placebo/erlotinib group; all 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. Most 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 reported 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 randomisation was 4.6 months, and most 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. Data monitoring committee reviewed the safety and efficacy data at predefined enrolment and event intervals throughout the study. Following a DMC analysis that showed no difference in superiority between the linsitinib/erlotinib and placebo/erlotinib groups, 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

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* (%)[a]			
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 status 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 (s.d.)	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 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* (%)	102 (100)	103 (100)	205 (100)
Neoadjuvant	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; s.d. = 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)	1.20	0.409
Median, days (95% CI)	381 (316–672)	421 (367–NR)	(0.777, 1.853)	
Best overall response, *n* (%)			NA	NA
Complete response	1 (1.0)	0 (0)		
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)	(4.07–5.94)		

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.

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.

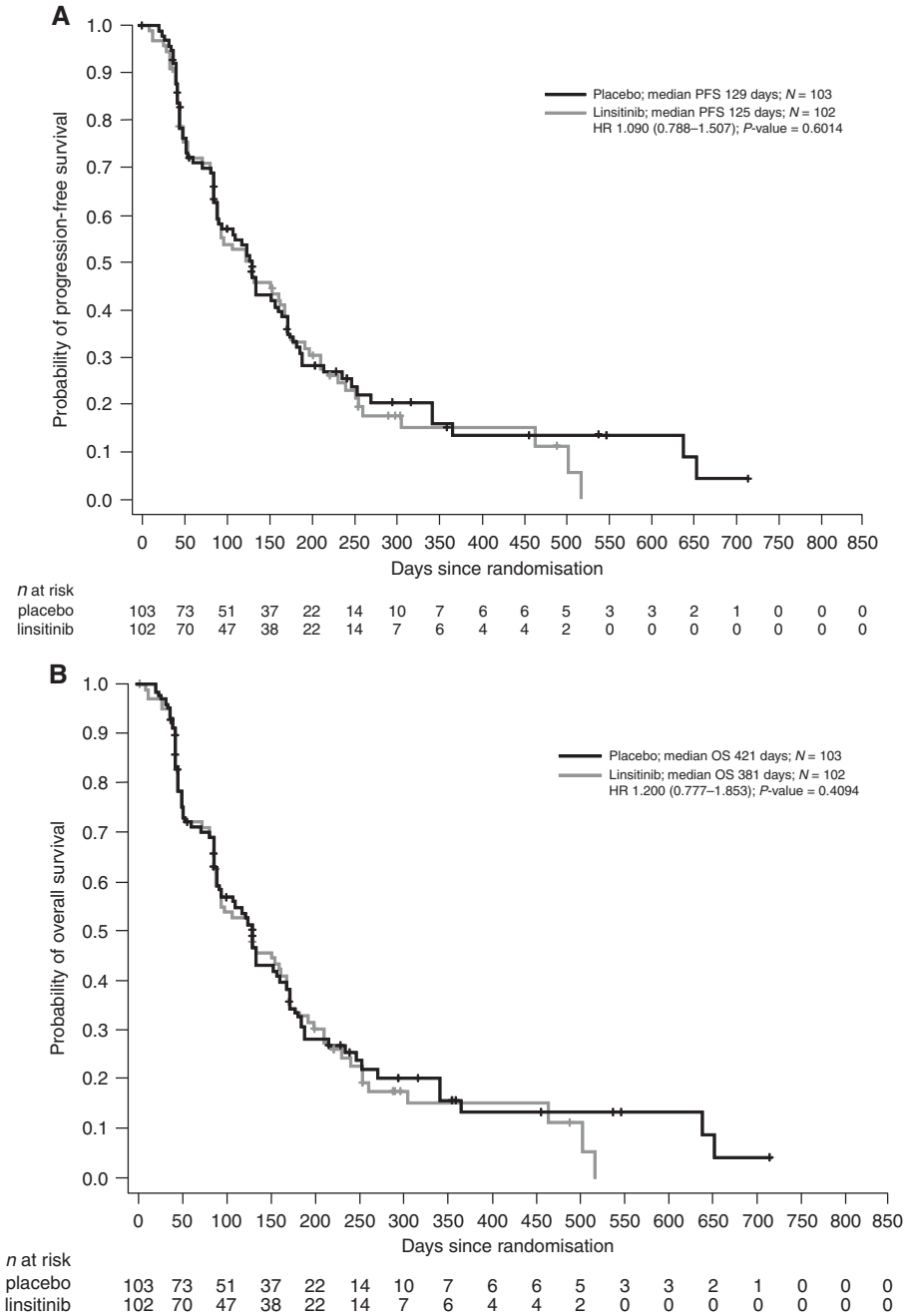

Figure 1. Progression-free survival (A) and overall survival (B), full analysis set. CI = confidence interval; HR = hazard ratio.

In the linsitinib/erlotinib arm, one patient achieved CR and 15 achieved PR, whereas in placebo/erlotinib group, 12 patients achieved PR and none achieved CR (Table 2).

Median linsitinib plasma concentrations at predose and 4 h in all TPs are listed in Table 4. Predose concentrations of erlotinib at steady state (TP2 and TP3) were similar in both treatment groups (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 signalling 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 predose plasma IGF-1 concentrations increased from 40 ng ml^{-1} in TP1 to 65 ng ml^{-1} in TP4, suggesting a pharmacodynamic effect.

With respect to analysis of tissue biomarkers that may have influenced efficacy, 90 patients treated with linsitinib/erlotinib and 92 patients treated with placebo/erlotinib had 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 receiving linsitinib/erlotinib and six patients

Table 3. Subgroup analysis and biomarker subgroup analysis of PFS

	Linsitinib/erlotinib ($n=102$)			Placebo/erlotinib ($n=103$)			
	N	Events n (%)	Median in days	N	Events n (%)	Median in days	HR, linsitinib *vs* placebo (95% CI)
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)
$\geqslant 65$	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							
$\geqslant$ 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: CI = confidence interval; ND = not determined; EGFR = epidermal growth factor receptor; HR = hazard ratio.
[a]Subgroup analysis of the full analysis set, which includes any patient who received at least one dose of linsitinib.
[b]Biomarker subgroup analysis of patients who had sufficient tissue/plasma samples for analysis among similar evaluable patients.

receiving 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, favouring 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 $\geqslant 20\%$ of patients in either group) for linsitinib/erlotinib *vs* placebo/erlotinib were rash/drug eruption (67.0 *vs* 58.4%), diarrhoea (44.0 *vs* 32.7%), decreased appetite (30.0 *vs* 20.8%), and nausea (22.0 *vs* 18.8%). Grade 3/4 TEAEs of rash/drug eruption (8.0%) and diarrhoea (5.0%) occurred in $\geqslant 5\%$ of patients treated with linsitinib/erlotinib. There were no grade 3/4 TEAEs in $\geqslant 5\%$ of patients treated with placebo/erlotinib.

Treatment-related AEs were more frequent in patients treated with linsitinib/erlotinib *vs* placebo/erlotinib (93 *vs* 87.1%, respectively). 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 diarrhoea (38.0 *vs* 28.7%) (Table 5). A higher proportion of patients receiving linsitinib/erlotinib had treatment-related SAEs (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 in those treated with placebo/erlotinib (10.9%). Of these patients, eight in the linsitinib/erlotinib group and three 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 patients (36.0%) in the linsitinib/erlotinib group and 29 patients (28.7%) in the placebo/erlotinib group. Serious treatment-related AEs were reported in 15 patients (15.0%) receiving linsitinib/erlotinib and eight patients (7.9%) receiving placebo/erlotinib.

Adverse events of special interest, including renal, hepatic, cardiac, glycaemic, and neurologic AEs, were also investigated. Overall, six patients (6.0%) receiving linsitinib/erlotinib and eight patients (7.9%) receiving placebo/erlotinib experienced renal and urinary disorders. In addition, 11 patients (11.0%) receiving linsitinib/erlotinib and 10 patients (9.9%) receiving placebo/

Table 4. Pharmacokinetics of erlotinib and linsitinib and pharmacodynamics of insulin-like growth factor-1

	Linsitinib/erlotinib				Placebo/erlotinib			
	n	Predose	*n*	4-h postdose	*n*	Predose	*n*	4-h postdose
Plasma concentration of erlotinib; median, ng ml^{-1} (range)								
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 (0–10 300)	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^{-1} (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^{-1} (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)
Diarrhoea	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)
Hyperglycaemia	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.

erlotinib experienced increased blood creatinine, and two patients (2.0%) receiving linsitinib/erlotinib and one patient (1.0%) receiving placebo/erlotinib experienced hepatobiliary disorders. For both treatment groups, most increases in liver enzymes and liver toxicity markers were low grade. Cardiac disorders (including QTcF interval prolongation) occurred in five patients (5.0%), each receiving either linsitinib/erlotinib or placebo/erlotinib. Serious cardiac TEAEs occurred in two patients (2%) receiving placebo/erlotinib, but not in patients receiving linsitinib/erlotinib. Hyperglycaemia occurred in 19 patients (19.0%) receiving linsitinib/erlotinib compared with eight patients (7.9%) receiving placebo/erlotinib; the events were treatment related in 15 patients (15.0%) receiving linsitinib/erlotinib (4.0%, grade 3/4) and four patients (4.0%) receiving placebo/erlotinib (all grades 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 that were considered serious: one patient (1.0%) receiving linsitinib/erlotinib and four patients (4.0%) receiving placebo/erlotinib.

Twelve deaths occurred during the study, none of which were deemed related to study treatment. In the linsitinib/erlotinib group, one patient died on Day 7 of study treatment due to bacterial pneumonia and six patients died within 30 days of the last administered dose. In patients who received placebo/erlotinib, five patients died within 30 days of last dose. The causes of death in patients receiving linsitinib/erlotinib were respiratory failure or distress ($n = 2$), pneumonia, dyspnoea, pulmonary embolism, abdominal sepsis, and disease progression ($n = 1$ each); and in the patients receiving placebo/erlotinib the causes were disease progression ($n = 2$), dyspnoea, respiratory failure, and neurological decompensation ($n = 1$ each).

DISCUSSION

This randomised 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 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 (Fassnacht *et al*, 2015; Jones *et al*, 2015; Puzanov *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 randomised to the linsitinib group, as were treatment discontinuations. As expected, due to the mechanisms of action of linsitinib, there was an increased incidence of hyperglycaemia in those receiving linsitinib, although none 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 the presence of sensitising 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 randomised 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 signalling between EGFR and IGF-1R pathways on inhibition of either pathway (Buck *et al*, 2008). Synergistic effects on cancer cell and tumour 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).

Pharmacokinetic data in this study indicated that predose concentrations of erlotinib were similar in both treatment groups, and the results were consistent with the Phase I study indicating a lack of substantial PK drug–drug interaction between erlotinib and linsitinib (Macaulay *et al*, 2016). 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 (Jones *et al*, 2015; Puzanov *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 (Ramalingam *et al*, 2011; Weickhardt *et al*, 2012; Scagliotti *et al*, 2015). IGF-1R signalling is inherently complex, involving cross-talk interactions with various feedback mechanisms, and compensatory and redundant signalling pathways in cancer cells (Jin *et al*, 2013). Therefore, 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 (Gerber and Schiller, 2013; Méry *et al*, 2015; Zhou *et al*, 2015). In the context of maintenance erlotinib, in the SATURN trial, the PFS was 44 weeks for a subgroup of patients with tumours 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 in both treatment arms (651 days in the placebo arm and 463 days in the linsitinib arm). There was no significant difference between the arms for this subgroup; however, the survival results observed likely reflect the greater efficacy of erlotinib for tumours with activating EGFR mutation. Therefore, 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 (Méry *et al*, 2015) and, more specifically, for maintenance treatment (Gerber and Schiller, 2013; Zhou *et al*, 2015). A difference in PFS was observed in patients with both EGFR wild-type and E-cadherin expression lower than the median, favouring the linsitinib group with median PFS linsitinib *vs* placebo of 128 *vs* 82 days (HR = 0.52, 95% CI, 0.29–0.94). However, due to the small sample sizes and multiple subgroup analyses, these results should be interpreted with caution. Other numeric differences in PFS, which did not reach statistical significance, were observed for patients aged $\geqslant$65 years in whom PFS was shorter for the linsitinib/erlotinib treatment arm compared with the placebo/erlotinib arm (127 days *vs* 171 days; HR = 1.30, 95% CI, 0.72–2.34). Additionally, the PFS was longer in the linsitinib/erlotinib treatment arm among patients who were former or current smokers, whereas the PFS was longer in the placebo/erlotinib arm among the never-smokers. This is consistent with the result for patients with activating EGFR mutation, which is likely to occur more frequently in the never-smokers. Similarly, never-smoking and EGFR mutation are known to be associated with adenocarcinoma biology (Gerber and Schiller, 2013; Zhou *et al*, 2015). In the current study, patients with squamous tumour histology had a median PFS of 127 days on linsitinib *vs* 113 days on placebo (HR = 0.67, 95% CI, 0.36–1.24). Finally, although numerically a very small subset ($n = 16$ for each arm), the PFS for patients with *KRAS* mutated positive tumours on linsitinib/erlotinib was superior to that for placebo/erlotinib treatment (128 *vs* 87 days, respectively; 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 patients in whom 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 *KRAS* mutant tumours. At present, 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 tumour 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 emphasise the need for development of mechanism-based therapies in clinical populations characterised 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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CONFLICT OF INTEREST

Tudor-Eliade Ciuleanu has served on an advisory board for Astellas, Amgen, AstraZeneca, Bristol-Myers Squibb, Janssen, Eli Lilly, Merck, Merck Sharp and Dohme, Pfizer, Roche, and Boehringer Ingelheim. JHK declares grant funding from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly and Company, and Roche. KP has served in an advisory role for Astellas and Roche. JC, SP, JMV, and DW were employed with Astellas at the time of the study. SA, JM, MT, and FB have no conflicts to disclose.

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