Cilengitide Combined with Cetuximab and Platinum-Based Chemotherapy as First-Line Treatment in Advanced Non-Small Cell Lung Cancer (NSCLC) Patients: Results of an Open-Label, Randomized, Controlled Phase 2 Study

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Abstract (299 of max 300 words)

PURPOSE: This multicenter, open-label, randomized, controlled, phase II study evaluated cilengitide in combination with cetuximab and platinum-based chemotherapy compared to cetuximab and chemotherapy alone as first-line treatment for patients with advanced non-small-cell lung cancer (NSCLC).

PATIENTS AND METHODS: Patients were randomised 1:1:1 to receive cetuximab plus platinum-based chemotherapy alone (control), or combined with cilengitide 2000 mg 1x/week (CIL-once) or 2x/week (CIL-twice). A study amendment triggered by new data led to the enrolment of patients with EGFR histoscore ≥200 only, and closure of the CIL-twice arm due to feasibility issues. Primary endpoint was progression-free survival (PFS; independent read); secondary endpoints included overall survival (OS), safety, and biomarker analyses.

RESULTS: Overall, 220 patients were randomized; data from CIL-once (n=85) and control (n=84) groups are reported. Overall PFS outcome (independent read) was improved in CIL-once vs control (6.2 vs 5.0 months; HR 0.72; p = 0.085), and more pronounced for patients with EGFR ≥200 (6.8 vs. 5.6 months respectively; HR, 0.57; p=0.0446). Sensitivity analysis of investigator read showed no difference in PFS. Median OS was 13.6 in CIL-once vs 9.7 months for control (HR 0.81; p = 0.265). In patients with EGFR ≥200, there was no difference in OS between CIL-once and control. No major differences in adverse events between CIL-once and control were reported; nausea (59% vs 56% respectively) and neutropaenia (54 vs 46%) were the most frequent. There was no increased incidence of thromboembolic events or haemorrhages in cilengitide-treated patients. αvβ3 and αvβ5 biomarker analysis did not reveal a prognostic correlation to PFS or OS, and was not predictive of treatment outcome.

CONCLUSIONS: The addition of cilengitide to cetuximab/chemotherapy indicated potential clinical activity with a significant PFS (independent read); however the observed inconsistencies across endpoints require additional investigations to further define a potential role of integrin inhibitors in NSCLC treatment.

Introduction

Lung cancer is the leading cause of cancer-related deaths, with approximately 85% of cases being non-small cell lung cancer (NSCLC) (Molina et al., 2008). In patients with advanced NSCLC, and in whom surgery is generally not a viable option, platinum-based combination chemotherapy remains the cornerstone of treatment (Lwin et al., 2013). The survival benefit offered by standard chemotherapy regimens is limited, with a median survival of 8–11 months in patients with advanced disease (Schiller et al., 2002; Fossella et al., 2003). In recent years, the recognition of important histological and molecular features of many tumors led to the development of targeted therapies, which have the potential to significantly impact the treatment paradigm for NSCLC (Blais and Hirsh, 2014). One of these features is the epidermal growth factor receptor (EGFR), activation of which has been implicated in tumorigenesis in NSCLC and has become a rational target for therapeutic intervention (Roengvoraphoj et al., 2013). Worldwide, the majority of patients with advanced NSCLC do not harbor activating mutations of the EGFR, and as a result such patients are unlikely to derive any more than a modest benefit from EGFR tyrosine kinase inhibitors, and only in the second line setting (Laurie and Goss, 2013; Lwin et al., 2013). As a consequence improving patient outcomes with chemotherapy regimens through rational drug combinations in conjunction with novel targeted agents remains critical.

Cetuximab is a recombinant human/mouse chimeric EGFR monoclonal antibody that inhibits EGFR activation (Li et al., 2005). In a large, randomized phase 3 trial (NCT00148798), patients with EGFR-detectable, advanced NSCLC demonstrated a survival advantage when cetuximab was added to first-line treatment with cisplatin/vinorelbine compared with chemotherapy alone (Pirker et al., 2009). A retrospective analysis of patients with high EGFR expression (histoscore ≥200) suggested the OS benefit for cetuximab plus chemotherapy was predominantly in this subgroup (Pirker et al., 2012).

Another anticancer therapeutic strategy gaining recognition involves targeting of integrins, which are transmembrane receptors involved in numerous cellular processes, including angiogenesis, cell survival, proliferation, and migration (Desgrosselier and Cheresh, 2010; Goodman and Picard, 2012). Cilengitide (EMD 121974) is a selective, competitive inhibitor of αvβ3 and αvβ5 integrins, targeting the tumor and its microenvironment (Smith et al., 2003).

In this phase 2 study, we evaluated the safety and efficacy of adding cilengitide to cetuximab and platinum-based chemotherapy as first-line treatment in patients with advanced NSCLC. The data from subgroup analysis of patients with high EGFR expression led to amendment of the study protocol, such that the focus of the study was on patients with EGFR histoscore ≥200 who are expected to benefit most from the addition of cetuximab to platinum-based chemotherapy (Pirker et al., 2012).

Methods

Patients and eligibility

Patients gave their written informed consent prior to enrollment of the study. The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization note for good clinical practice (ICH, Topic E6, 1996), and applicable regulatory requirements. Adults with histologically confirmed newly diagnosed NSCLC at either stage IIIb with documented malignant pleural effusion, or stage IV, with EGFR histoscore ≥200 on tumor tissue (added in protocol amendment) were eligible. Additional eligibility criteria are described in the **Supplementary Methods**.

Study design

This was a multicenter, open-label, randomized, controlled, Phase II study (NCT00842712; **Supplementary Figure 1**). Following a safety run-in during which a dose of 2000 mg cilengitide once-daily was found to be well tolerated in combination with platinum-based chemotherapy plus cetuximab, patients were randomized 1:1:1 to three treatment arms. CIL-once : cilengitide 2000 mg once-weekly (Days 1, 8 and 15 of every 3-week cycle) in combination with cetuximab 400 mg/m^2 as a 2-hour intravenous infusion (Day 1 of Cycle 1), followed by 250 mg/m^2 as a 1-hour infusion once-weekly (Days 8 and 15 of Cycle 1 and Days 1, 8 and 15 of all subsequent cycles) plus either cisplatin 80 mg/m^2 intravenous infusion on Day 1 of each cycle and vinorelbine 25 mg/m^2 intravenous infusion on Days 1 and 8, or cisplatin 75 mg/m^2 intravenous infusion on Day 1 of each cycle and gemcitabine 1250 mg/m^2 intravenous infusion on Days 1 and 8, of each 3-week cycle. CIL-twice: cilengitide 2000 mg twice-weekly (Days 1, 4, 8, 11, 15 and 18 of each 3-week cycle) in combination with cetuximab and platinum-based chemotherapy as for CIL-once. Control: cetuximab and platinum-based chemotherapy only as for CIL-once.

Patient enrolment commenced in February 2010. In December 2010, the protocol was amended to focus only on patients with high EGFR histoscore (EGFR expression ≥200). The CIL-twice group was

closed for feasibility reasons. Patients randomized to CIL-twice before the amendment (51 patients) continued to be treated as planned.

The choice of chemotherapy regimen was at the investigator's discretion. At the end of chemotherapy, patients continued with once-weekly cetuximab and cilengitide until radiographically documented progressive disease, unacceptable toxicity, or consent withdrawal. Patients who discontinued treatment without progressive disease remained in the trial, with response assessment continued every 6 weeks until disease progression or commencement of another anti-tumor treatment.

Outcome measures

The primary efficacy endpoint was progression-free survival (PFS), defined as time in months from randomization day to the first observation of radiologically confirmed disease progression or death, and based on Independent Review Committee (IRC) assessment of tumor response. A pre-specified sensitivity analysis was performed using an investigator read of tumor response. Secondary endpoint was efficacy in terms of overall survival (OS), safety, and biomarker analysis.

Analyses of efficacy variables were performed using the total intent-to-treat (ITT) analysis set, which included all patients randomized to treatment. Patients with EGFR histoscore ≥200 and those with EGFR histoscore <200 were considered as subgroups of the ITT analysis set.

Efficacy was assessed with the Kaplan-Meier product-limit method, with hazard ratios (HR) including 95% confidence intervals (CI) of both cilengitide arms relative to the control arm calculated using the Cox's proportional hazards model stratified by the selected first-line chemotherapy.

Safety analyses were based on the safety analysis set including all patients who received any dose of cilengitide, cetuximab or chemotherapy. Adverse events (AEs) were summarized according to the Medical Dictionary for Regulatory Activities (MedDRA) terms and their severity graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTC). Expression

(read-out: histoscores) of integrins αvβ3 and αvβ5 was determined on tumor and endothelial cells to investigate their predictive value in PFS and OS.

Results

Patients

Of 220 randomized patients who formed the ITT analysis set, 85 patients were assigned to the CIL-once arm, 51 patients to CIL-twice (closed), and 84 patients to the control arm: of these, 215 received at least one dose of trial medication and were considered in the safety analysis. The results outlined herein are concerned only with the CIL-once and control arms. **Table 1** summarizes patient demographics and baseline characteristics, which were well balanced between the arms.

Efficacy

In the primary efficacy endpoint analysis, median PFS was 6.2 months (95% CI, 5.6–7.4) in the CIL-once arm compared with 5.0 months (95% CI, 4.2–5.6; HR, 0.718 [95% CI, 0.492–1.048]; p=0.0845) in the control arm based on IRC assessment (**Figure 1A**). Likewise, for patients with EGFR ≥200, the PFS was improved in the CIL-once arm at 6.8 months compared with 5.6 months in the control arm (HR, 0.566; 95% CI, 0.323–0.993; p=0.0446; **Figure 1B**). Among patients with EGFR histoscore <200, median PFS was longer at 7.1 months in the CIL-once arm compared with 3.2 months in the control arm, however with high variability due to low subgroup size (HR, 0.731; 95% CI, 0.372–1.438; p=0.3628).

The sensitivity analyses of PFS per investigator assessment found similar PFS overall between the CIL-once (5.6 months) and control (5.3 months) arms, with a HR of 0.909 (95% CI, 0.642–1.286; p=0.5912). Also, the investigator read of patients with EGFR ≥200 found no difference in median PFS between the CIL-once and control arms (5.8 vs. 5.5 months; HR, 0.980; 95% CI, 0.603–1.593; p=0.9348). Among patients with EGFR <200, the investigator read showed prolonged PFS in the CIL-once compared with the control arm, again with high variability (6.5 vs. 3.2 months; HR, 0.814; 95% CI, 0.424–1.560; p=0.5348).

PFS subgroup analysis (**Supplementary Figure S2A**) showed a non-significant trend towards an improved response to cilengitide therapy in patients with squamous cell cancer (HR, 0.52 [0.22,

1.19]) compared with patients with adenocarcinoma or other histologies. Females and patients ≥65 years, showed increased benefit from CIL-once treatment compared with chemotherapy treatment only (HR, 0.45 [0.23, 0.87] and 0.33 [0.13, 0.84], for females and age ≥65 years respectively).

Median OS overall was longer at 13.6 months in the CIL-once arm compared with 9.7 months in the control arm (HR, 0.813; 95% CI, 0.564–1.171; p=0.2648; **Figure 2A**). For patients with high EGFR expression, median OS was similar in the CIL-once (13.2 months) and control arm (11.8 months; HR, 0.952; 95% CI, 0.561–1.614; p=0.855; **Figure 2B**). Among patients with lower EGFR score, median OS was longer in the CIL-once arm(14.3 months) compared with control (8.6 months; HR, 0.814; 95% CI, 0.411–1.616; p=0.5564).

Unlike the PFS subgroup analysis, OS subgroup analysis on histology did not show improved OS in cilengitide treated patients with squamous cell cancer (HR, 0.68 [0.34, 1.37]) compared with patients with other histologies (**Supplementary Figure S2B**).

Safety

The AE distribution was rather similar between CIL-once vs control, in terms of any AE (both 100%), any NCI-CTC toxicity grade 3 or 4 (84.7% vs 88.8%), study treatment related (94.1% vs 95.0%), or study treatment related NCI-CTC toxicity grade 3 or 4 (70.6% vs 71.3%).

The most common AEs of any grade and regardless of relationship occurring more frequently in the CIL-once arm included nausea, neutropenia, and anemia (**Table 2**). The number of patients who experienced hemorrhages (18.8% vs. 26.3%) and thromboembolic events (31.8% vs. 28.8%) was not increased with cilengitide treatment. Serious AEs were reported in 42 (49.4%) patients treated with CIL-once compared with 45 (56.3%) patients in the control arm. Most commonly reported serious AEs were pulmonary embolism, general physical health deterioration, and neutropenia. AEs leading

to death occurred in 8 (9.4%) patients in the CIL-once arm and 7 (8.8%) patients in the control arm. In two patients in each arm, AEs leading to death were treatment related.

Biomarker analysis

Thirty-six patients in the CIL-once arm and 40 patients in the control arm were included in the biomarker analysis, with similar demographics between the two (data not shown). The distribution of biomarkers was comparable between the two groups, with patients in both arms exhibiting very low positive signal for αvβ3 expressing tumors. **Table 3** summarizes the expression of the biomarkers linked to OS and PFS. The small sample size did not allow correlation between expression level of the assessed biomarkers to OS or PFS, nor did it allow for predicting clinical benefit.

Discussion

This open-label, randomized, controlled phase 2 study in patients with advanced NSCLC demonstrated that the addition of once-weekly cilengitide to a cetuximab/chemotherapy combination results in potential clinical activity compared with cetuximab/chemotherapy alone. This study shows that in the overall population the primary outcome PFS (per independent read) was prolonged in patients who received cilengitide compared with control. This activity trend in PFS was more pronounced in the subpopulation of patients with high EGFR expression. However, the results were inconsistent with the sensitivity analysis PFS for the investigator read as well as with the OS results. Addition of cilengitide also resulted overall in a trend for prolonged OS, although the magnitude of the treatment effect was more pronounced for overall and low EGFR expression populations as compared to patients with high levels of EGFR.

Triggered by the emergence of data indicating that an EGFR histoscore of ≥200 predicts improved survival with the addition of cetuximab to first-line chemotherapy in patients with advanced NSCLC (Pirker et al., 2012), the CERTO study was amended. The protocol amendment switched the focus from recruiting patients with EGFR-positive NSCLC to patients with high EGFR expression only. This would have allowed to continue development if cetuximab had gained regulatory approval for the treatment of NSCLC patients with high EGFR histoscore. In the present study however, the impact of EGFR histoscore on cetuximab and the overall outcome of the combination treatment remains unclear.

Although designed as a three-arm study, the results presented herein summarize only the data for patients assigned to the CIL-once and control arms as consequence of the protocol amendment that stopped any further recruitment to the CIL-twice arm. This change was implemented after the first 51 patients entered the arm when it was recognized that there might be feasibility issues related to twice-weekly administration of cilengitide in real-world clinical practice.

EGFR is commonly overexpressed in NSCLC EGFR IS NOT PROGNOSTIC – STUDIES SUGGEST BOTH IMPROVED AND REDUCED SURVIVALS and is thus a rational therapeutic target. Current strategies for inhibition of EGFR include tyrosine kinase inhibitors, monoclonal antibodies, ligand-linked toxins, and antisense approaches (Gridelli et al., 2009; Roengvoraphoj et al., 2013). Most strategies are limited as they are dependent on mutational drivers of EGFR activation, whilst the majority of patients with advanced NSCLC have a wildtype phenotype (Laurie and Goss, 2013). Cetuximab has shown a benefit in OS when combined with platinum-based chemotherapy in treatment-naïve patients with EGFR-positive NSCLC (Pirker et al., 2009). The improvement in OS associated with cetuximab NOT TRUE ANYMORE I.E. AFATINIB IMROVES SURVIVAL IN EGFR DEL19 PATIENTS VS CHEMOTHERAPY may relate to antibody-mediated receptor internalization and turnover, resulting in non-kinase activity (Gridelli et al., 2009). The addition of an integrin inhibitor to cetuximab/chemotherapy in the present clinical trial recognizes the need for therapies that target different components of tumorigenesis, which in the case of integrins involves interactions between tumor cells and the extracellular matrix, angiogenesis, and tumor cell migration, invasion, proliferation and survival (Manegold et al., 2013). In a previous trial for treatment of NSCLC, median PFS and OS were similar for single-agent docetaxel and single-agent cilengitide at a dose of 600 mg/m^2, providing a basis for further investigation of cilengitide as a combination partner in this indication (Manegold et al., 2013). In glioblastoma, single-agent cilengitide was well tolerated and demonstrated modest antitumor activity in newly diagnosed (Nabors et al., 2012) and recurrent disease (Reardon et al., 2008), however failed to provide benefit in the pivotal phase III trial (Stupp et al., 2014). As a consequence the further development of cilengitide was terminated. Still the results of this trial may support further developments of other compounds for treatment of NSCLC.

The safety profile of the combination of cilengitide with cetuximab and platinum-based chemotherapy was as expected, with no safety concerns revealed for cilengitide. In particular, there was no evidence to suggest that cilengitide treatment increased the risk of bleeding or thromboembolic events.

Exploratory biomarker analysis investigating the levels of avß3 and avß5 integrins in epithelia and tumors, suggested that the presence of these biomarkers was not prognostically correlated with either PFS or OS, and was not predictive of a treatment effect for cilengitide. However, the sample size was small preventing interpretation of this data. This analysis needs to be performed in a larger population.

In conclusion, the data presented suggests a trend towards potentially improved PFS and OS for cilengitide treatment of patients with advanced NSCLC when compared with the control arm. However, the inconsistent treatment effect (independent versus investigator read; PFS versus OS in high EGFR patient group), the combination with cetuximab and the potential impact of the EGFR histoscore on the cetuximab/chemotherapy background all add to the complexity of the trial. Additional investigations are needed to further define the role of integrin inhibitors such as cilengitide in the first-line treatment of advanced NSCLC.

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Tables

Table 1. Patient baseline characteristics and demographics (ITT population)

Characteristic	CIL-once (Arm A) N=85	Control (Arm C) N=84
Median age, years (range)	58.6 (40–81)	59.8 (38–75)
Gender, n (%)		
Male	51 (60.0)	57 (67.9)
Female	34 (40.0)	27 (32.1)
Performance status score, n (%)		
0	37 (43.5)	42 (50.0)
≥1	48 (56.5)	41 (48.8)
Missing	0	1 (1.2)
EGFR expression, n (%)		
≥200	48 (56.5)	44 (52.4)
<200	24 (28.2)	24 (28.6)
Missing	13 (15.3)	16 (19.0)
Histology, n (%)		
Adenocarcinoma	58 (68.2)	53 (63.1)
Squamous cell carcinoma	22 (25.9)	19 (22.6)
Other	5 (5.9)	12 (14.3)
Median time from diagnosis to first informed consent, months (range)	0.7 (0.4–12.5)	0.6 (0.0–33.0)
First-line chemotherapy, n (%)		
Cisplatin + vinorelbine	14 (16.5)	14 (16.7)
Cisplatin + gemcitabine	71 (83.5)	70 (83.3)

CIL, cilengitide; EGFR, epidermal growth factor receptor; ITT, intention to treat.

Table 2. AEs experienced by ≥20% of patients overall*

	Cil Once (n=85)		No Cil (n=80)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Any AE	85 (100%)	72 (84.7%)	80 (100%)	71 (88.8%)
Anemia	34 (40.0%)	4 (4.7)	24 (30.0)	9 (11.3)
Leukopenia	20 (23.5)	9 (10.6)	10 (12.5)	4 (5.0)
Neutropenia	46 (54.1)	32 (37.6)	37 (46.3)	26 (32.5)
Thrombocytopenia	29 (34.1)	14 (16.5)	25 (31.3)	14 (17.5)
Constipation	17 (20.0)	-	20 (25.0)	-
Diarrhea	22 (25.9)	2 (2.4)	23 (28.8)	-
Nausea	50 (58.8)	5 (5.9)	43 (53.8)	6 (7.5)
Asthenia	20 (23.5)	2 (2.4)	23 (28.8)	4 (5.0)
Fatigue	29 (34.1)	3 (3.5)	20 (25.0)	3 (3.8)
Decreased appetite	30 (35.3)	4 (4.7)	21 (26.3)	2 (2.5)
Hypomagnesaemia	18 (21.2)	4 (4.7)	7 (8.8)	2 (2.5)
Acne	19 (22.4)	1 (1.2)	17 (21.3)	1 (1.3)
Dermatitis Acneiform	17 (20.0)	5 (5.9)	16 (20.0)	5 (6.3)
Rash	35 (41.2)	6 (7.1)	29 (36.3)	4 (5.0)

*AEs by preferred term (MedDRA) and graded by NCI-CTC.

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; NCI-CTC, National Cancer Institute Common Terminology Criteria for Adverse Events

Table 3. Summary of clinical endpoints (BM population)*

	PFS (IRC assessment)		OS	
	Median (months) CIL-once vs. control	HR (95% CI)	Median (months) CIL-once vs. control	HR (95% CI)
avß3 endothelium				
≤ median (n=43)	6.2 vs. 5.6	0.94 (0.43–2.08)	10.6 vs. 13.3	1.02 (0.45–2.27)
> median (n=27)	5.9 vs. 4.1	0.35 (0.13–0.92)	12.5 vs. 7.6	0.89 (0.37–2.13)
avß3 tumor				
≤ median (n=65)**	5.9 vs. 5.0	0.70 (0.39–1.28)	12.5 vs. 11.9	0.89 (0.49–1.61)
avß5 endothelium				
≤ median (n=38)	12.4 vs. 4.4	0.52 (0.22–1.23)	18.6 vs. 7.9	0.51 (0.22–1.20)
> median (n=31)	5.9 vs. 5.6	1.19 (0.48–2.96)	9.2 vs. 29.1	2.27 (0.80–6.38)
avß5 tumor				
≤ median (n=39)	6.2 vs. 5.0	0.86 (0.38–1.94)	14.3 vs. 7.9	0.77 (0.36–1.68)
> median (n=34)	5.9 vs. 4.4	0.68 (0.29–1.60)	10.4 vs. 7.3	0.85 (0.38–1.92)

*Results of the number of evaluable patients per analysis are presented; **Number of patients with avß3 tumor > median (n=9) is too low to be analyzed. BM, biomarker; CI, confidence interval; CIL, cilengitide; HR, hazard ratio; IRC, independent review committee; PFS, progression-free survival; OS, overall survival.

Figure Legends

Figure 1. Overall PFS (IRC assessment). Figure 2A shows the overall ITT population, figure 2B shows the ITT population for patients with EGFR ≥ 200. CI, confidence interval; CIL, cilengitide; HR, hazard ratio; IRC, independent review committee; EGFR, epidermal growth factor receptor; ITT, intention to treat; PFS, progress-free survival.

Figure 2. Overall survival. Figure 3A shows the overall ITT population, figure 3B shows the ITT population for patients with EGFR ≥ 200. CI, confidence interval; CIL, cilengitide; EGFR, epidermal growth factor receptor; HR, hazard ratio; ITT, intention to treat.

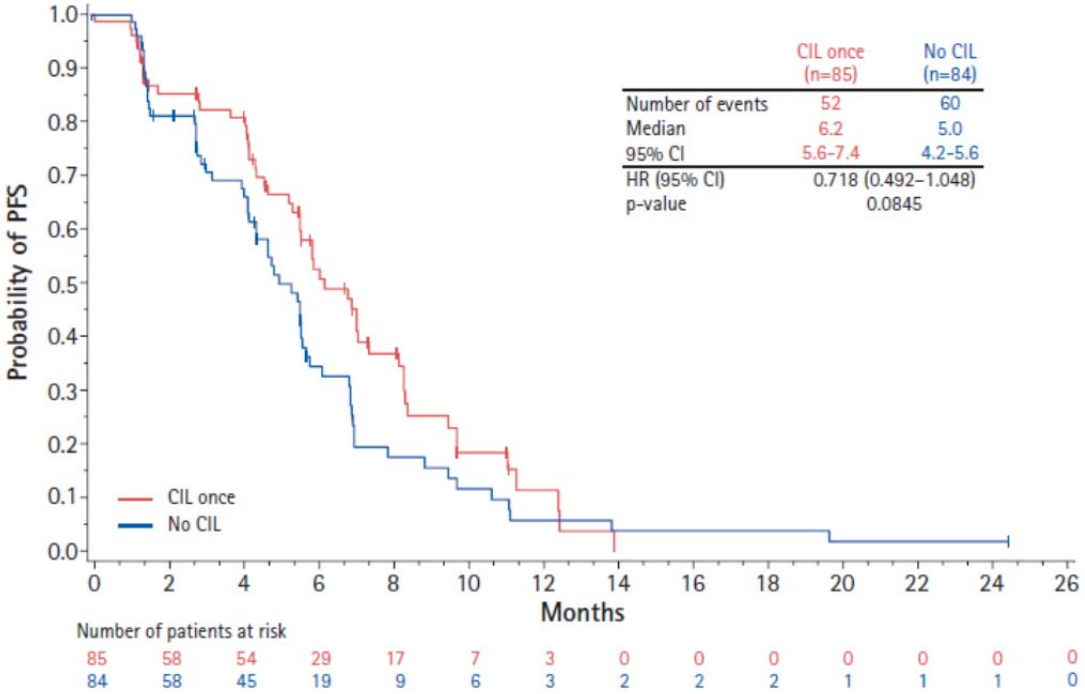
Supplementary Figure S1. Study design. ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; R, randomization.

Supplementary Figure S2. PFS (3A) and OS (3B) subgroup analysis

Figures [All figures will be redrawn according to target journal requirements prior to manuscript submission.]

Figure 1. Overall PFS (IRC assessment).

A.



B.

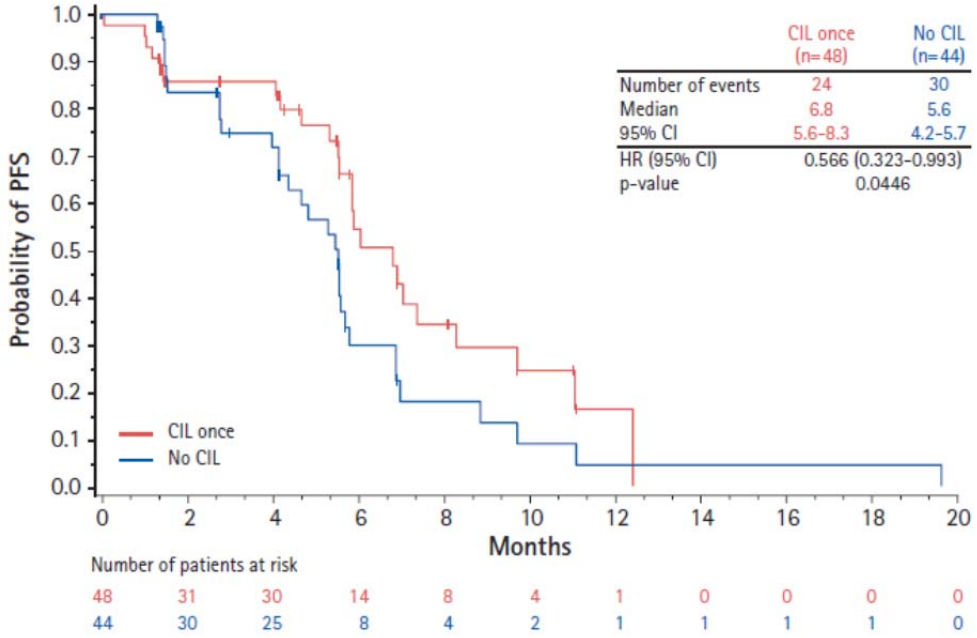
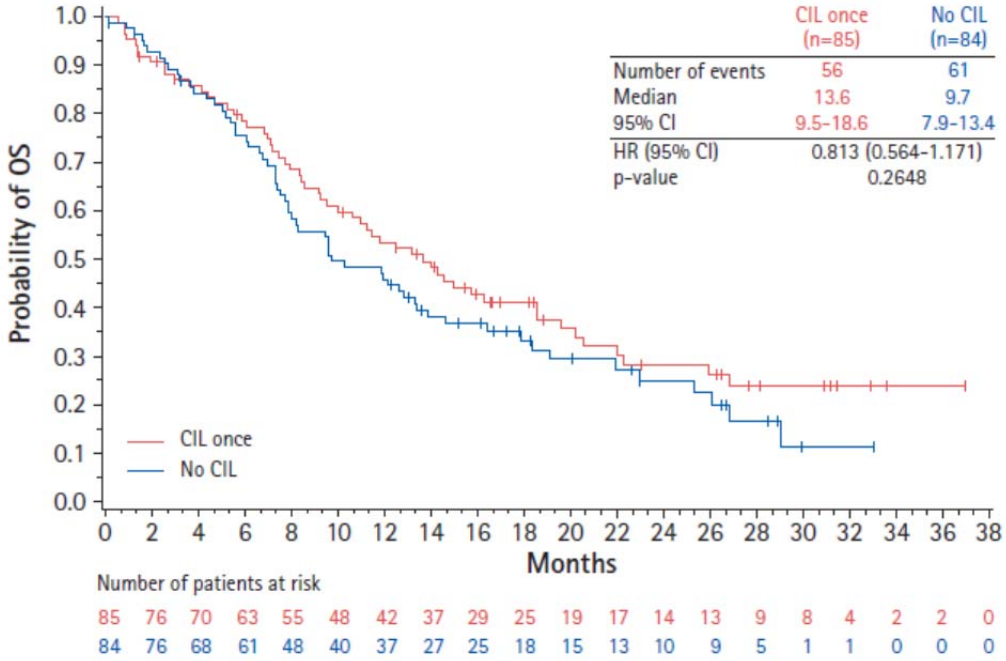


Figure 2. Overall survival.

A



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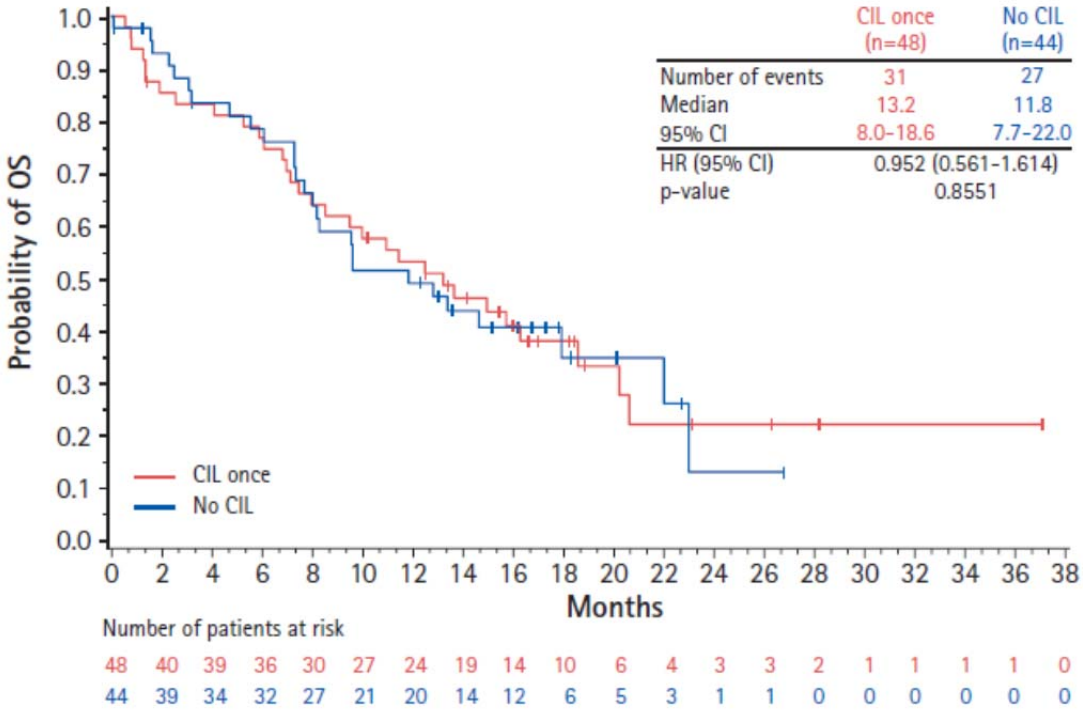


Supplementary Files

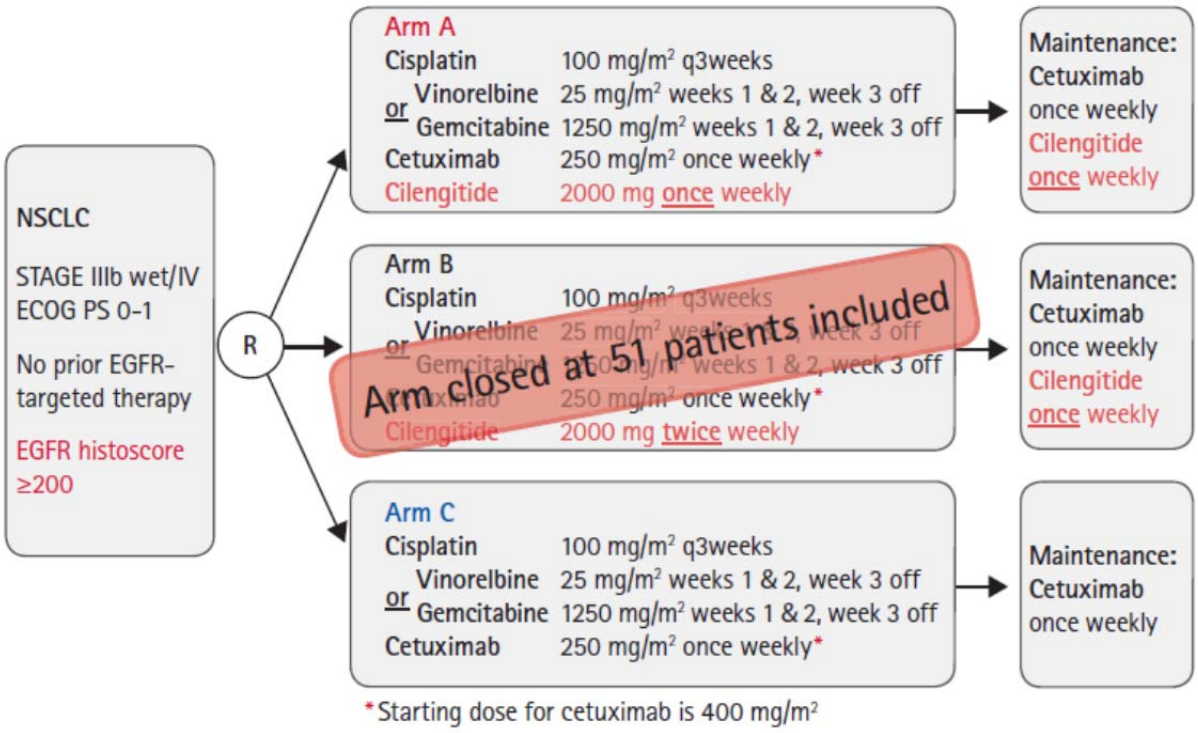
Supplementary Methods

Patient eligibility criteria

In addition to the main inclusion criteria, eligible patients were required to have archived tumor material samples for central histology and further biomarker research, ≥1 radiographically documented measurable lesion in a previously non-irradiated area according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria, and an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1.

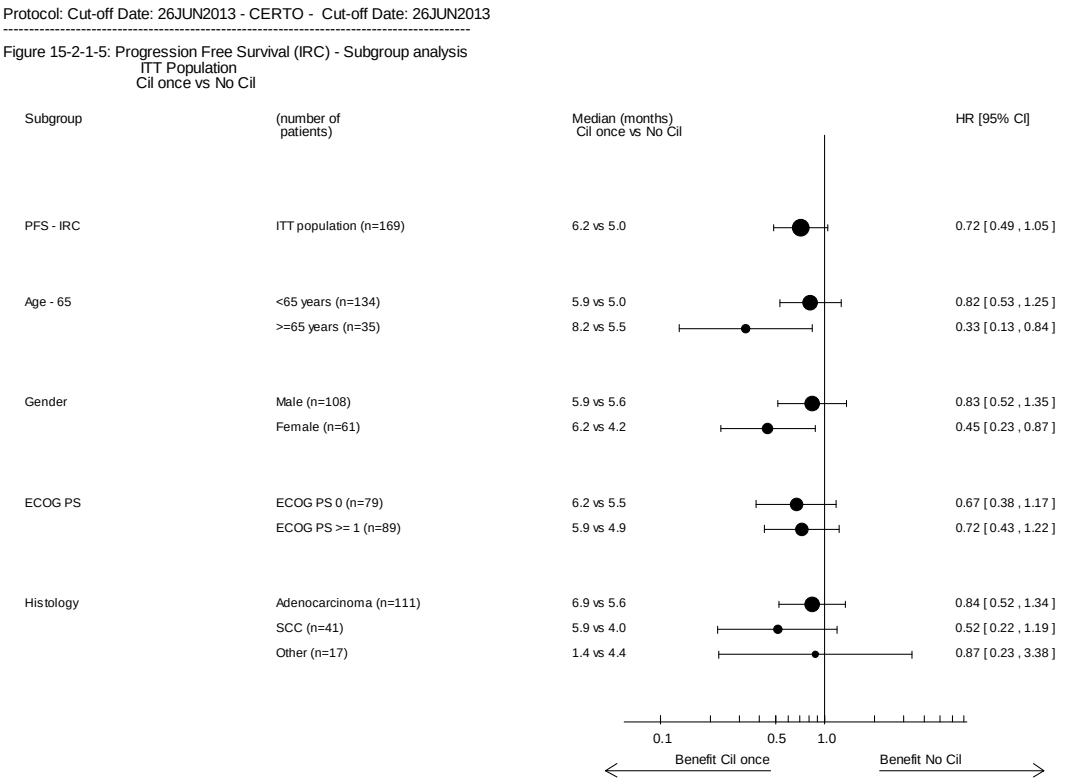
Key exclusion criteria included: prior therapy with an anti-EGFR or anti-vascular endothelial growth factor receptor treatment; previous NSCLC-related chemotherapy; history of brain metastasis or leptomeningeal disease; radiotherapy, major surgery or intake of investigational drug within 30 days of trial entry; concurrent chronic immunosuppressive or hormone anti-cancer therapy; history of coagulation disorder associated with bleeding, recurrent or recent thrombotic events, or hemoptysis related to bronchopulmonary cancer; or recent peptic ulcer disease.

Supplementary Figure S1. Study design.



Supplementary Figure S2. PFS (3A) and OS (3B) subgroup analysis

A.



B.