Lung Cancer xxx (2012) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

# Efficacy and safety of maintenance erlotinib in Asian patients with advanced non-small-cell lung cancer: A subanalysis of the phase III, randomized SATURN study

Yi-Long Wu[a,*,1], Joo-Hang Kim[b,1], Keunchil Park[c], Adel Zaatar[d], Gaëlle Klingelschmitt[e], Christina Ng[f]

[a] Guangdong Lung Cancer Institute, Guangdong General Hospital & Guangdong Academy of Medical Sciences, 106 Zhongshan Er Road, Guangzhou 510080, China
[b] Yonsei Cancer Centre, Yonsei University College of Medicine, Seoul, Republic of Korea
[c] Samsung Medical Centre, Seoul, Republic of Korea
[d] Gleneagles Medical Centre, Penang, Malaysia
[e] F. Hoffmann-La Roche Ltd, Basel, Switzerland
[f] Sunway Medical Centre, Kuala Lumpur, Malaysia

ARTICLE INFO

*Article history:*
Received 26 September 2011
Received in revised form 16 March 2012
Accepted 17 March 2012

*Keywords:*
Asian patients
Non-small-cell lung cancer
NSCLC
Erlotinib
Maintenance therapy
Phase III trial

ABSTRACT

Maintenance therapy, commenced immediately after the completion of first-line chemotherapy, is a promising strategy for improving treatment outcomes in patients with non-small-cell lung cancer (NSCLC). The global phase III SequentiAl Tarceva in UnResectable NSCLC (SATURN) study evaluated the efficacy and safety of the epidermal growth factor receptor (EGFR) tyrosine-kinase inhibitor erlotinib as maintenance treatment in NSCLC patients without progression after first-line chemotherapy. We report a retrospective subanalysis of Asian patients enrolled in SATURN.

Patients with advanced NSCLC with no evidence of progression after four cycles of chemotherapy were randomized to receive erlotinib 150 mg/day or placebo, until progressive disease or limiting toxicity. The co-primary endpoints of SATURN were progression-free survival (PFS) in all patients and in those with positive EGFR immunohistochemistry (IHC) status. Secondary endpoints included overall survival (OS), disease control rate, safety, quality of life (QoL) and biomarker analyses.

In total, 126 patients from East and South-East Asian centers were randomized (14% of the intent-to-treat population): 88 from Korea, 28 from China and 10 from Malaysia; one patient was excluded from this analysis due to Indian ethnicity. PFS was significantly prolonged in the erlotinib treatment arm, both overall (hazard ratio [HR]: 0.57; $p = 0.0067$) and in patients with EGFR IHC-positive disease (HR = 0.50; $p = 0.0057$). There was a trend towards an increase in OS, which reached statistical significance in the EGFR IHC-positive subgroup ($p = 0.0233$). The overall response rate was significantly higher with erlotinib compared with placebo (24% versus 5%; $p = 0.0025$). Erlotinib was generally well tolerated and had no negative impact on QoL in this subpopulation. The most common treatment-related adverse events were rash, diarrhea and pruritus.

Erlotinib was effective and well tolerated in Asian patients, producing benefits consistent with those observed in the overall SATURN population. Maintenance treatment with erlotinib appears to be a useful option for the management of Asian patients with advanced NSCLC without progression after first-line chemotherapy.



## 1. Introduction

In patients with advanced non-small-cell lung cancer (NSCLC), successive cycles of first-line platinum doublet chemotherapy are typically associated with cumulative toxicity and no increase in benefit [1,2]. As a result, chemotherapy is usually halted after 4–6 cycles. A treatment break has traditionally been provided after first-line chemotherapy, with second-line treatment introduced on disease progression. However, in this scenario, a high proportion of patients with NSCLC (30–50%) never commence second-line treatment, mainly due to deterioration in clinical status and rapidly progressing disease [3–5]. Maintenance therapy is an alternative approach in which active therapy is started immediately after first-line chemotherapy with no treatment break. The rationale for this approach is that continuous treatment exposure may delay disease

* Corresponding author. Tel.: +86 20 838 77855; fax: +86 20 838 27712.
*E-mail address:* syylwu@live.cn (Y.-L. Wu).
[1] Yi-Long Wu and Joo-Hang Kim are joint lead authors on this manuscript.

0169-5002/$ – see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.lungcan.2012.03.012

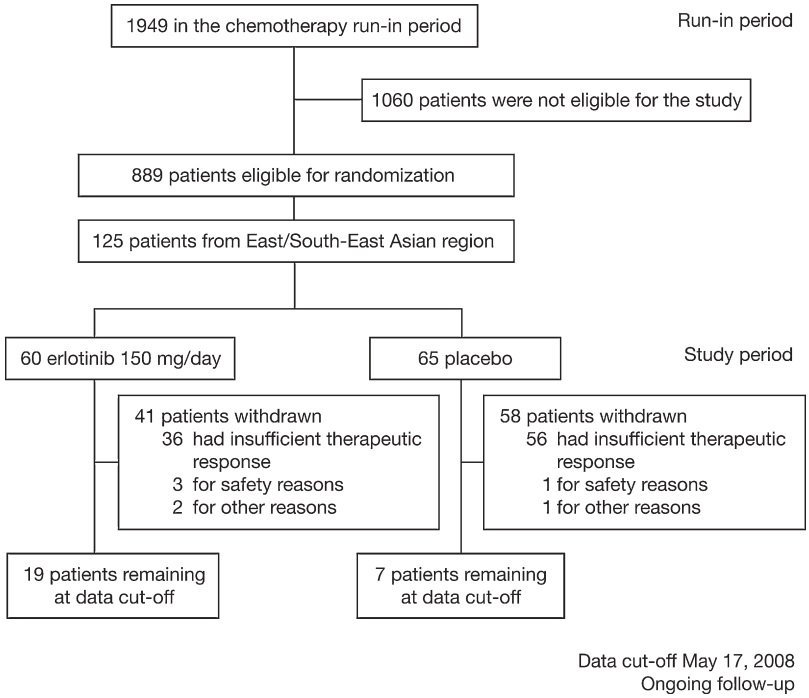


**Fig. 1.** SATURN study design showing Asian enrollees.

progression and improve survival. In recent years, maintenance therapy has become an established paradigm in NSCLC management [6–8].

Studies of maintenance therapy in NSCLC have been stimulated by the availability of various novel agents suited to use in maintenance regimens. Recent studies employing immediate switching to docetaxel [3] or pemetrexed [4] after first-line chemotherapy for NSCLC reported benefits in terms of progression-free survival (PFS) and overall survival (OS) versus delaying second-line treatment until disease progression, while continuation of non-platinum components of first-line therapy has produced promising results with agents such as bevacizumab [7,8], cetuximab [9,10], gemcitabine [11,12] and pemetrexed [13].

The oral epidermal growth factor receptor (EGFR) tyrosine-kinase inhibitor (TKI) erlotinib is an established option for the second-line treatment of patients with advanced NSCLC [14,15], producing survival benefits similar to those of approved second-line chemotherapy agents, docetaxel and pemetrexed [16]. The efficacy of erlotinib was established in the randomized, placebo-controlled BR.21 trial in 731 patients with advanced NSCLC treated with at least one previous line of chemotherapy [17]. In this study, erlotinib significantly prolonged survival, delayed symptom progression and improved quality of life (QoL) compared with placebo, and was effective across a range of patient subgroups [4].

The phase III SequentiAl Tarceva in UnResectable NSCLC (SATURN; BO18192) study of erlotinib as maintenance treatment in patients with non-progressive disease after first-line chemotherapy evaluated the efficacy and safety of erlotinib in this setting. The overall results of SATURN demonstrated significant improvements in PFS and OS with erlotinib versus placebo. These benefits were evident across clinical and biomarker subgroups, without impairment of QoL [18,19]. Of note, only a small proportion of patients in the placebo arm (21%) received an EGFR TKI following study discontinuation. Asian patients have been reported to gain a greater benefit from EGFR TKIs compared with non-Asian patients [20,21], because of their increased predisposition to *EGFR* mutations [22,23]. We report results of a retrospective subanalysis of efficacy and safety in Asian patients enrolled in the SATURN study, to evaluate the potential value of erlotinib maintenance therapy in this population.

## 2. Patients and methods

### 2.1. Study design

SATURN was an international, placebo-controlled study of erlotinib maintenance treatment after first-line chemotherapy for NSCLC. This retrospective subanalysis evaluated the results for patients enrolled into SATURN from East and South-East Asian centers. Fig. 1 summarizes the study design. After completion of four cycles of chemotherapy (run-in period), eligible patients with no evidence of progressive disease were randomized to treatment with erlotinib 150 mg/day or placebo. The allocated treatment was continued until the development of progressive disease or unacceptable toxicity.

The full study methodology, including eligibility criteria for the run-in and randomization phases, has been published in the primary manuscript [18], and is presented in abbreviated form here. Inclusion criteria for the run-in (chemotherapy) phase included: age ≥18 years; presence of histologically documented, measurable (by Response Evaluation Criteria In Solid Tumors [RECIST]), advanced, recurrent or metastatic NSCLC; and an available tumor sample. Criteria for entry into the randomization phase included: completion of four cycles of standard platinum-doublet chemotherapy without disease progression (achievement of complete response [CR], partial response [PR] or stable disease [SD]); an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 or 1; adequate renal, hepatic and hematologic function; and a negative pregnancy test in females of child-bearing age. The main exclusion criteria were: previous exposure to anti-EGFR treatment; the presence of uncontrolled, symptomatic brain metastases; and history of any malignancy within the past 5 years (except for carcinoma in situ).

Please cite this article in press as: Wu Y-L, et al. Efficacy and safety of maintenance erlotinib in Asian patients with advanced non-small-cell lung cancer: A subanalysis of the phase III, randomized SATURN study. Lung Cancer (2012), doi:10.1016/j.lungcan.2012.03.012

**Table 1**
Baseline characteristics for the Asian subpopulation and the overall population of SATURN.

| *n* (%) unless otherwise specified | SATURN Asian subpopulation | | Overall SATURN population | |
|---|---|---|---|---|
| | Erlotinib (*n* = 60) | Placebo (*n* = 65) | Erlotinib (*n* = 438) | Placebo (*n* = 451) |
| Median age, years (range) | 55 (33–73) | 54 (30–77) | 60 (33–83) | 60 (30–81) |
| Gender | | | | |
| Male | 40 (67) | 42 (65) | 321 (73) | 338 (75) |
| Female | 20 (33) | 23 (35) | 117 (27) | 113 (25) |
| Histology | | | | |
| Adenocarcinoma/BAC | 40 (67) | 34 (52) | 205 (47) | 198 (44) |
| Squamous cell carcinoma | 6 (10) | 22 (34) | 166 (38) | 194 (43) |
| Other | 14 (23) | 9 (14) | 67 (15) | 59 (13) |
| Stage | | | | |
| IIIB | 11 (18) | 15 (23) | 116 (26) | 109 (24) |
| IV | 49 (82) | 50 (77) | 322 (74) | 342 (76) |
| ECOG PS | | | | |
| 0 | 10 (17) | 18 (28) | 135 (31) | 145 (32) |
| 1 | 50 (83) | 47 (72) | 303 (69) | 306 (68) |
| Smoking status | | | | |
| Current smoker | 21 (35) | 28 (43) | 239 (55) | 254 (56) |
| Former smoker | 15 (25) | 12 (18) | 122 (28) | 122 (27) |
| Never smoker | 24 (40) | 25 (38) | 77 (18) | 75 (17) |
| EGFR IHC status | | | | |
| Positive | 40 (67) | 54 (83) | 308 (70) | 313 (69) |
| Negative | 13 (22) | 8 (12) | 62 (14) | 59 (13) |
| Unknown | 7 (12) | 3 (5) | 68 (16) | 79 (18) |
| *EGFR* mutation status | | | | |
| Activating mutation | 4 (7) | 8 (12) | 22 (5) | 27 (6) |
| Other mutation (including resistance mutations) | 1 (2) | 0 (0) | 7 (2) | 2 (<1) |
| Wild-type | 10 (17) | 18 (28) | 199 (45) | 189 (42) |
| Indeterminate | 6 (10) | 1 (2) | 33 (8) | 39 (9) |
| Missing | 39 (65) | 38 (58) | 177 (40) | 194 (43) |
| Response to first-line therapy | | | | |
| CR | 0 (0) | 0 (0) | 1 (<1) | 1 (<1) |
| PR | 25 (42) | 29 (45) | 183 (42) | 209 (47) |
| SD | 34 (57) | 34 (52) | 252 (58) | 235 (52) |

BAC, basal adenocarcinoma.

SATURN employed the co-primary endpoints of PFS in all patients (the intent-to-treat [ITT] population) and PFS in the EGFR immunohistochemistry (IHC)-positive subgroup (i.e., patients whose tumors had a high level of EGFR protein expression as assessed by IHC). Secondary endpoints consisted of PFS in the IHC-negative subgroup, OS in all patients and in the EGFR IHC-positive subgroup, best response, time-to-progression, safety and QoL. Extensive biomarker analyses were also conducted.

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and the protocol was approved by local ethics committees at each enrollment center. All patients enrolled in the study gave informed consent for participation and also for provision of tumor samples. The study is registered with ClinicalTrials.gov, study number NCT00556712.

### 2.2. Procedures and assessments

Data on baseline characteristics were collected at the time of randomization, after completion of initial chemotherapy. In terms of study demographics, Asian ethnic origin included patients from East and South-East Asia and the Indian subcontinent. Smoking status of patients was categorized as follows: patients with a smoking history of <100 cigarettes in their lifetime were designated never smokers; those who had smoked ≥100 cigarettes, but had not smoked within the last year were classified as former smokers; and the remaining patients were classified as current smokers.

Tumor assessments were done by computed tomography (CT) scan, spiral CT scan, or magnetic resonance imaging at initial screening, after completion of chemotherapy (study baseline), then at 6-week intervals until week 48, and subsequently every 12 weeks until disease progression was confirmed. Tumor response was classified by use of RECIST 1.0. QoL was assessed using the Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire at 6-week intervals until week 48 and every 12 weeks thereafter.

Collection of tumor tissue for biomarker assessment was mandatory during screening. EGFR IHC status was determined using the Dako EGFR pharmDx kit, and tumors were considered EGFR IHC-positive if 10% or more of tumor cells showed membranous staining of any intensity. Unfortunately the number of *EGFR* mutation-positive Asian patients in this subanalysis was insufficient to allow investigation of PFS and OS in relation to *EGFR* mutation status. This reflects difficulties in obtaining sufficient quantities of tumor tissue to allow the large number of biomarker tests specified in the SATURN protocol to be carried out. Full details of the methodology of the molecular analyses are included in a separate report of the biomarker results from the study [19].

Adverse events (AEs) and serious AEs were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 3.0. In patients with AEs, dose reductions in 50 mg steps and interruptions for up to 2 weeks were permitted. On disease progression, the choice of further treatment was at the investigator's discretion. Unblinding was permitted only if the investigator judged that an EGFR TKI was the only possible second-line treatment option. The trial sponsor remained blinded to this information.

### 2.3. Statistical analysis

The evaluation of PFS included objective progression and clinical progression. Basic comparison of the two treatment groups was done using a two-sided, log-rank test, without adjustment for

Please cite this article in press as: Wu Y-L, et al. Efficacy and safety of maintenance erlotinib in Asian patients with advanced non-small-cell lung cancer: A subanalysis of the phase III, randomized SATURN study. Lung Cancer (2012), doi:10.1016/j.lungcan.2012.03.012

**Table 2**
Comparison of survival outcomes in the Asian subpopulation and the overall population of SATURN.

| | SATURN Asian population | | Overall SATURN population | |
|---|---|---|---|---|
| | HR (95% CI) | Log-rank *p* value | HR (95% CI) | Log-rank *p* value |
| PFS | | | | |
| All patients | 0.57 (0.37–0.86) | 0.0067 | 0.71 (0.62–0.82) | <0.0001 |
| EGFR IHC-positive | 0.50 (0.30–0.83) | 0.0057 | 0.69 (0.58–0.82) | <0.0001 |
| OS | | | | |
| All patients | 0.67 (0.42–1.07) | 0.0931 | 0.81 (0.70–0.95) | 0.0088 |
| EGFR IHC-positive | 0.53 (0.30–0.93) | 0.0233 | 0.77 (0.64–0.93) | 0.0063 |

further potential prognostic factors. All time-to-event endpoints were measured from time of randomization (the completion of chemotherapy). The trial was designed with 80% power at the two-sided 3% significance level, assuming a 25% improvement in PFS (hazard ratio [HR] = 0.80) for the ITT population and a 33% improvement in PFS (HR = 0.75) in the EGFR IHC-positive subgroup. The alpha allocation was 3% for all patients and 2% for the EGFR IHC-positive subgroup, a total of 5%. The trial was controlled for alpha spend due to interim analysis by the Lan-DeMets alpha spending function with an O'Brien-Fleming boundary.

As this is a report of a subpopulation from the SATURN study, further subgroup analyses by clinical characteristics, biomarkers, or response to first-line chemotherapy are not reported, as the subgroups would include too few patients to provide any meaningful statistical analysis or clinical interpretation.

## 3. Results

### 3.1. Patient demographics

A total of 1949 patients received at least one dose of standard doublet chemotherapy in the run-in phase prior to randomization, of whom 889 patients had CR/PR or SD after four cycles and were randomized to receive erlotinib or placebo (the overall ITT study population). In the initial phase, 241 patients were enrolled from the East and South-East Asian region, including 177 from Korea, 46 from China and 18 from Malaysia. Of these, 126 patients were randomized to receive study treatment (88 patients from Korea, 28 from China and 10 from Malaysia). For the purposes of this analysis, one patient was excluded as they were of Indian ethnicity, leaving 125 patients or 14% of the global ITT population who received either erlotinib ($n = 60$) or placebo ($n = 65$). The baseline characteristics of the Asian subpopulation and the overall SATURN patient population are compared in Table 1.

### 3.2. Efficacy analysis

Erlotinib maintenance therapy significantly prolonged PFS compared with placebo in the overall Asian subpopulation (HR = 0.57; 95% confidence interval [CI]: 0.37–0.86; $p = 0.0067$; cut-off date May 2008) and also in the subgroup of Asian patients with EGFR IHC-positive status (HR = 0.50; 95% CI: 0.30–0.83; $p = 0.0057$) (Table 2; Fig. 2). There was a non-significant trend towards increased OS in the erlotinib treatment arm in the Asian subpopulation (HR = 0.67; 95% CI: 0.42–1.07; $p = 0.0931$; cut-off date May 2009), which reached statistical significance in Asian patients with EGFR IHC-positive status (HR = 0.53; 95% CI: 0.30–0.93; $p = 0.0233$) (Table 2; Fig. 2).

Time-to-progression of disease was also significantly prolonged with erlotinib versus placebo in the Asian subpopulation (HR = 0.54; 95% CI: 0.35–0.83; $p = 0.0038$). There were no significant differences in the 12-week disease control rate (DCR) between the treatment groups for the Asian subpopulation (47.5% with erlotinib versus

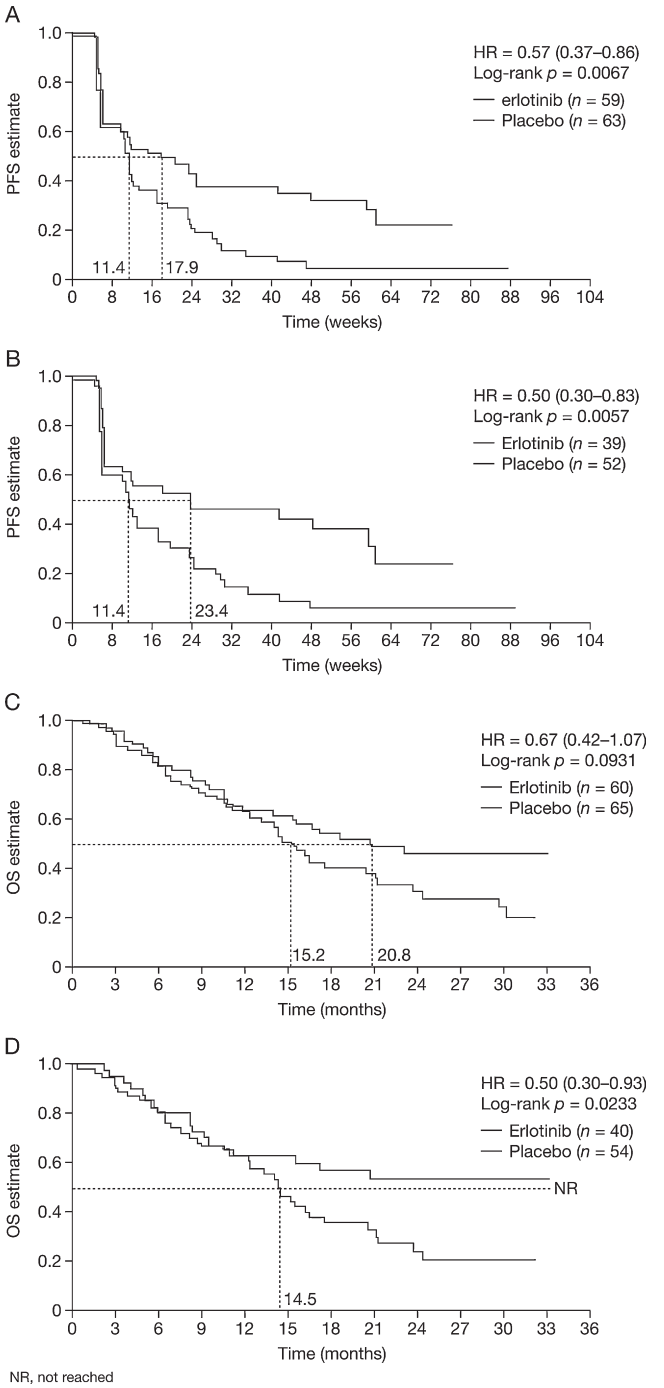


**Fig. 2.** Kaplan–Meier curves for the Asian subpopulation of SATURN showing: PFS in all patients (A), PFS in EGFR IHC-positive populations (B), OS in all patients (C) and OS in EGFR IHC-positive populations (D).

Please cite this article in press as: Wu Y-L, et al. Efficacy and safety of maintenance erlotinib in Asian patients with advanced non-small-cell lung cancer: A subanalysis of the phase III, randomized SATURN study. Lung Cancer (2012), doi:10.1016/j.lungcan.2012.03.012

**Table 3**
Summary of main safety findings for the Asian subpopulation of the SATURN study.

| *n* (%) | Erlotinib (*n* = 59) | Placebo (*n* = 63) |
|---|---|---|
| Severe AEs (grade 3/4) | 16(27) | 7(11) |
| Serious treatment-related AEs | 4(7) | 0(0) |
| Withdrawal due to treatment-related AEs | 2(3) | 0(0) |
| AEs leading to dose modification/interruption | 14(24) | 3(5) |
| Treatment-related AEs occurring in ≥10% of patients | | |
| Rash[a] | 45(76) | 8(13) |
| Pruritus | 16(27) | 3(5) |
| Acne | 9(15) | 0(0) |
| Dry skin | 6(10) | 1(2) |
| Diarrhea | 17(30) | 2(3) |
| Paronychia | 12(20) | 0(0) |

[a] Refers only to the Medical Dictionary for Regulatory Activities (MedDRA)-defined term of rash.

34.9% with placebo). However, erlotinib treatment produced a significantly higher overall response rate compared with placebo (23.7% versus 4.8%; $p = 0.0025$).

### 3.3. Safety and QoL analysis

Maintenance treatment with erlotinib was well tolerated in Asian patients enrolled in SATURN, and no unexpected safety issues were encountered. The safety analysis includes 59 patients in the erlotinib arm and 63 in the placebo arm; three patients were excluded as they did not receive any study treatment. The most common AEs in erlotinib-treated patients were skin problems, such as rash and pruritus, and diarrhea (Table 3). Compared with placebo, erlotinib treatment was associated with a higher incidence of severe (grade 3/4) AEs (27% versus 11%) and serious treatment-related AEs (7% versus 0%). Four erlotinib-treated patients had a serious treatment-related AE: one had grade 2 interstitial lung disease (ILD); one had a grade 3 alanine aminotransferase increase and a grade 2 aspartate aminotransferase increase; one had grade 3 diarrhea and one had grade 5 ILD. Only two Asian patients withdrew from treatment due to treatment-related AEs.

The HR for time-to-symptomatic progression with erlotinib versus placebo was 0.89 and the HR for time to deterioration in Trial Outcome Index with erlotinib versus placebo was 0.93. The time to deterioration in QoL did not differ significantly between the erlotinib and placebo treatment groups (median 12 versus 10 months; HR = 1.03; 95% CI: 0.65–1.64; $p = 0.9018$), indicating that erlotinib maintenance therapy did not negatively affect QoL compared with a break from active treatment.

The most commonly used post-study treatments in the Asian subpopulation, at the time of the OS data cut-off in May 2009, were antimetabolites (including pemetrexed, gemcitabine and tegafur), taxanes (including docetaxel and paclitaxel) and EGFR TKIs (Table 4). Post-treatment EGFR TKIs were received by 54% of patients in the placebo arm and 37% of patients in the erlotinib arm.

**Table 4**
Post-study treatments in the Asian subpopulation of the SATURN study occurring in >10% of patients in either treatment arm (data cut-off May 2009).

| *n* (%) | Erlotinib (*n* = 60) | Placebo (*n* = 65) |
|---|---|---|
| All classes[a] | 54(90) | 55(85) |
| Antimetabolites | 29(48) | 32(49) |
| Taxanes | 26(43) | 29(45) |
| EGFR TKIs | 22(37) | 35(54) |
| Surgical and medical procedures | 16(27) | 18(28) |
| Antineoplastic agents | 17(28) | 13(20) |
| Platinum compounds | 5(8) | 11(17) |
| Topoisomerase inhibitors | 2(3) | 9(14) |

[a] Number of patients with at least one treatment.

## 4. Discussion

In the overall population of the phase III SATURN study of erlotinib maintenance therapy, erlotinib significantly improved PFS and OS compared with placebo (HR = 0.71 and 0.81, respectively) [18]. The findings of this preplanned subanalysis show that Asian patients also derived benefit from maintenance therapy with erlotinib after first-line, platinum-based chemotherapy. Unfortunately, the small number of patients enrolled into SATURN from Asian centers means that this subanalysis is underpowered to detect statistically significant differences between the two treatment arms. The effect of erlotinib on OS did not reach significance; however, for most other endpoints statistically significant differences were reached in favor of erlotinib. These included prolonged PFS in the Asian subpopulation as a whole (50% increase in median PFS), and in the subgroup with EGFR IHC-positive status (100% increase), as well as an increased response rate versus placebo in this population (24% versus 5%).

The survival benefits of erlotinib maintenance therapy in the Asian subpopulation were consistent with those in the global SATURN population, for both the ITT populations and the EGFR IHC-positive Asian subgroup. Nevertheless, the HR for OS in the Asian subpopulation (HR = 0.67) was lower than that reported for the overall SATURN ITT population (HR = 0.81).

A possible explanation for this may be the small number of patients evaluated, together with the high rate of censoring, particularly in erlotinib-treated patients, of whom approximately 50% had not undergone an event at the time of analysis. In addition, OS results might have been confounded by differences in second- and third-line treatments between the SATURN Asian and ITT populations. In the Asian subpopulation, 54% of patients in the placebo arm and 37% of patients in the erlotinib arm received EGFR TKIs post-study, compared with 21% and 11% of patients, respectively, in the SATURN ITT population.

This subanalysis has several limitations, and the data are inherently less robust than those of the SATURN ITT population due to the retrospective nature of the analysis. Although South-East Asia was included as a stratification region in the randomization of patients for SATURN, certain differences between treatment groups among the Asian subpopulation might have been clinically significant. Compared with patients receiving placebo, the erlotinib treatment arm included a higher proportion of patients with an ECOG PS of 1 (83% versus 72%), and a lower proportion of patients with EGFR IHC-positive status (67% versus 83%) (Table 1), which would predict a poorer disease outcome from EGFR TKI treatment [21,24]. However, the erlotinib group also included a higher number of patients with the more treatment-responsive adenocarcinoma pathology (67% versus 52%). In addition, 40% of erlotinib-treated patients in the Asian subanalysis were never smokers, compared with just 18% of patients receiving erlotinib in the SATURN ITT population, a factor that may also increase the likelihood of response to treatment.

Patients of Asian ethnicity with NSCLC appear to be particularly responsive to EGFR TKIs, a predictive association thought be related to the higher incidence of activating *EGFR* mutations in Asian compared with Western populations (approximately two- to three-fold higher) [24–27]. Unfortunately, a further limitation of this subanalysis was the lack of sample material, which prevented any meaningful evaluation of efficacy outcomes by *EGFR* mutation status. Previous studies have shown that tumors with *EGFR* mutations are highly responsive to EGFR TKIs [24,28,29]. Similarly, in the overall SATURN population, the estimated HR for PFS in the *EGFR*

Please cite this article in press as: Wu Y-L, et al. Efficacy and safety of maintenance erlotinib in Asian patients with advanced non-small-cell lung cancer: A subanalysis of the phase III, randomized SATURN study. Lung Cancer (2012), doi:10.1016/j.lungcan.2012.03.012

mutation-positive population was 0.10 for erlotinib versus placebo, indicating a substantial benefit. The phase III OPTIMAL study investigated the first-line use of erlotinib in 154 Chinese patients with *EGFR* mutation-positive NSCLC, and reported significant improvements in PFS versus chemotherapy (HR = 0.16, 95% CI: 0.10–0.26; $p < 0.0001$) [30], indicating that earlier use of EGFR TKI therapy is warranted in this patient subgroup. As noted earlier, the relatively small size of the Asian subpopulation means that any further subdivision by *EGFR* mutation-positive versus wild-type status would have limited the viability of any conclusions.

Erlotinib was generally well tolerated in Asian patients and did not impair QoL compared with placebo, which is consistent with the overall SATURN findings. This is an important consideration in this treatment setting, since a pivotal argument for offering treatment breaks after first-line chemotherapy is that this approach allows patients to recover from the often-debilitating effects of cytotoxic chemotherapy. Use of a less toxic agent for maintenance treatment can enable patients to recover from chemotherapy, while continuing to receive treatment able to produce clinically meaningful improvements in disease status and survival.

The findings of this subanalysis in a highly selected subpopulation demonstrate a PFS benefit of erlotinib maintenance treatment in Asian patients with advanced NSCLC. Whether it is preferable to use a proven agent such as erlotinib as traditional second-line treatment or as maintenance therapy remains a matter of conjecture [18]. However, due to the possibility of rapid progression after first-line chemotherapy, the maintenance approach should at least be considered when evaluating treatment options.

## 5. Conclusions

This preplanned subanalysis of the SATURN study suggests that the clinical benefits of maintenance treatment with erlotinib observed in the overall SATURN population are also seen in patients of Asian ethnicity. Erlotinib maintenance treatment thus represents a novel treatment option in Asian patients with advanced NSCLC who have not progressed after first-line chemotherapy.

## Conflict of interest statement

Yi-Long Wu received honoraria from F. Hoffmann-La Roche, AstraZeneca, Eli Lilly and Pfizer to serve as a speaker. Joo-Hang Kim received a grant for research from F. Hoffmann-La Roche for the SATURN trial. Gaëlle Klingelschmitt is a permanent employee of F. Hoffmann-La Roche and was the statistician of the SATURN study. Keunchil Park, Adel Zaatar and Christina Ng declare no conflicts of interest.

## Acknowledgments

The authors would like to acknowledge all the patients involved in this study, as well as their families; they would also like to thank all of their fellow SATURN investigators for their contributions to this study. The SATURN study was sponsored by F. Hoffmann-La Roche. Support for third-party writing assistance for this manuscript was provided by F. Hoffmann-La Roche.

## References

[1] Socinski MA, Morris DE, Masters GA, Lilenbaum R, American College of Chest Physicians. Chemotherapeutic management of stage IV non-small cell lung cancer. Chest 2003;123(1 Suppl.):226S–43S.
[2] Park JO, Kim SW, Ahn JS, Suh C, Lee JS, Jang JS, et al. Phase III trial of two versus four additional cycles in patients who are nonprogressive after two cycles of platinum-based chemotherapy in non-small cell lung cancer. J Clin Oncol 2007;25:5233–9.
[3] Fidias PM, Dakhil SR, Lyss A, Loesch DM, Waterhouse DM, Bromund JL, et al. Phase III study of immediate compared with delayed docetaxel after front-line therapy with gemcitabine plus carboplatin in advanced non-small-cell lung cancer. J Clin Oncol 2008;27:591–8.
[4] Ciuleanu T, Brodowicz T, Zielinski C, Kim JH, Krzakowski M, Laack E, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomized, double-blind phase 3 study. Lancet 2009;374:1432–40.
[5] Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 2008;26:3543–51.
[6] Belani CP, Liao J. Maintenance therapy for non-small-cell lung cancer. Lancet 2010;375:281–2.
[7] Reck M, van Pawel J, Zatloukal P, Ramlau R, Gorbounova V, Hirsh V, et al. Phase III trial of gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAiL. J Clin Oncol 2009;27:1227–34.
[8] Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 2006;355:2542–50.
[9] Belani CP, Schreeder MT, Steis RG, Guidice RA, Marsland TA, Butler EH, et al. Cetuximab in combination with carboplatin and docetaxel for patients with metastatic or advanced-stage nonsmall cell lung cancer. A multicenter phase 2 study. Cancer 2008;113:2512–7.
[10] Pirker R, Pereira JR, Szczesna A, von Pawel J, Krzakowski M, Ramlau R, et al. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomized phase III trial. Lancet 2009;373:1525–31.
[11] Brodowicz T, Krzakowski M, Zwitter M, Tzekova V, Ramlau R, Ghilezan N, et al. Cisplatin and gemcitabine first-line chemotherapy followed by maintenance gemcitabine or best supportive care in advanced non-small cell lung cancer: a phase III trial. Lung Cancer 2006;52:155–63.
[12] Perol M, Chouaid C, Milleron BJ, Gervais R, Barlesi F, Westeel V, et al. Maintenance with either gemcitabine or erlotinib versus observation with predefined second-line treatment after cisplatin-gemcitabine induction chemotherapy in advanced NSCLC: IFCT-GFPC 0502 phase III study. J Clin Oncol 2010;28(15 Suppl.):540s [Abstract 7507].
[13] Paz-Ares LG, De Marinis F, Dediu M, Thomas M, Pujol J, Bidoli P, et al. Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial. Lancet Oncol 2012;13:247–55.
[14] Azzoli CG, Baker Jr S, Temin S, Pao W, Aliff T, Brahmer J, et al. American Society of Clinical Oncology Clinical Practice Guideline update on chemotherapy for stage IV non-small-cell lung cancer. J Clin Oncol 2009;27:6251–66.
[15] D'Addario G, Felip E, on behalf of the ESMO Guidelines Working Group. Non-small-cell lung cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 2009;20(Suppl. 4):68–70.
[16] Ramalingam S, Sandler AB. Salvage therapy for advanced non-small cell lung cancer: factors influencing treatment selection. Oncologist 2006;11:655–65.
[17] Shepherd F, Rodrigues Pereira J, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 2005;353:123–32.
[18] Cappuzzo F, Ciuleanu T, Stelmakh L, Cicenas S, Szczésna A, Juhász E, et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomized, placebo-controlled phase 3 study. Lancet Oncol 2010;11:521–9.
[19] Brugger W, Triller N, Blasinka-Morawiec S, Curescu S, Sakalauskas R, Manikhas GM, et al. Prospective molecular marker analyses of EGFR and KRAS from a randomized, placebo-controlled study of erlotinib maintenance therapy in advanced non-small-cell lung cancer. J Clin Oncol 2011;29:4113–20.
[20] Chang A, Parikh P, Thongprasert S, Tan EH, Perng RP, Ganzon D, et al. Gefitinib (IRESSA) in patients of Asian origin with refractory advanced non-small cell lung cancer: subset analysis from the ISEL study. J Thorac Oncol 2006;1:847–55.
[21] Mok T, Wu Y-L, Au JS-K, Zhou C, Zhang L, Perng RP, et al. Efficacy and safety of erlotinib in 1242 East/South-East Asian patients with advanced non-small cell lung cancer. J Thorac Oncol 2010;5:1609–15.
[22] Shigematsu H, Lin L, Takahashi T, Nomura M, Suzuki M, Wistuba II, et al. Clinical and biological features associated with epidermal growth factor receptor gene mutations in lung cancers. J Natl Cancer Inst 2005;97:339–46.
[23] Wu J-Y, Shih J-Y, Chen K-Y, Yang C-H, Yu C-J, Yang P-C. Gefitinib therapy in patients with advanced non-small cell lung cancer with or without testing for epidermal growth factor receptor (EGFR) mutations. Medicine 2011;90:159–67.
[24] Rosell R, Moran T, Queralt C, Porta R, Cardenal F, Camps C, et al. Screening for epidermal growth factor receptor mutations in lung cancer. N Engl J Med 2009;361:958–67.
[25] Kosaka T, Yatabe Y, Onozato T, Mitsudomi T. Prognostic implication of the EGFR gene mutations in a large cohort of Japanese patients with early stage lung adenocarcinoma. J Clin Oncol 2007;25(Suppl. 18):402S [Abstract 7574].
[26] Wu Y-L, Zhong W-Z, Li L, Zhang XT, Zhang L, Zhou CC, et al. Epidermal growth factor receptor mutations and their correlation with gefitinib therapy in patients with non-small cell lung cancer: a meta-analysis based on updated individual patient data from six medical centers in mainland China. J Thorac Oncol 2007;2:430–9.

Please cite this article in press as: Wu Y-L, et al. Efficacy and safety of maintenance erlotinib in Asian patients with advanced non-small-cell lung cancer: A subanalysis of the phase III, randomized SATURN study. Lung Cancer (2012), doi:10.1016/j.lungcan.2012.03.012

[27] Tsao MS, Sakurada A, Cutz JC, Zhu CQ, Kamel-Reid S, Squire J, et al. Erlotinib in lung cancer—molecular and clinical predictors of outcome. N Engl J Med 2005;353:133–44.
[28] Mok T, Wu Y-L, Thongprasert S, Yang CH, Chu DT, Saijo N, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947–57.
[29] Murray S, Dahabreh IJ, Linardou H, Manoloukos M, Bafaloukos D, Kosmidis P. Somatic mutations of the tyrosine-kinase domain of epidermal growth factor receptor and tyrosine-kinase inhibitor response to TKIs in non-small-cell lung cancer: an analytical database. J Thorac Oncol 2008;3:832–9.
[30] Zhou C, Wu Y-L, Chen G, Feng J, Liu X, Wang C, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced *EGFR* mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol 2011;12:735–42.

Please cite this article in press as: Wu Y-L, et al. Efficacy and safety of maintenance erlotinib in Asian patients with advanced non-small-cell lung cancer: A subanalysis of the phase III, randomized SATURN study. Lung Cancer (2012), doi:10.1016/j.lungcan.2012.03.012