Survival benefit with erlotinib maintenance therapy in patients with advanced non-small-cell lung cancer (NSCLC) according to response to first-line chemotherapy

B. Coudert1*, T. Ciuleanu2, K. Park3, Y.-L. Wu4, G. Giaccone5, W. Brugger6, P. Gopalakrishna7 & F. Cappuzzo8 SATURN Investigators

1Medical Oncology Department, Centre Georges François Leclerc, Dijon, France; 2Institute of Oncology Ion Chiricuta, Cluj-Napoca, Romania; 3Department of Medicine Samsung Medical Centre, Sungkyunkwan University School of Medicine, Seoul, Korea; 4Guangdong Lung Cancer Institute, Guangdong General Hospital, Guangzhou, China; 5Medical Oncology Branch National Institutes of Health, Bethesda, USA; 6Department of Hematology/Oncology Schwarzwald-Baar Clinic, Teaching Hospital, University of Freiburg, Villingen-Schwenningen, Germany; 7Department of Pharma Development, Roche Products Ltd., Welwyn Garden City, UK; 8Department of Oncology-Hematology, Ospedale Civile di Livorno, Livorno, Italy

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Background: In the placebo-controlled phase III SATURN study, maintenance erlotinib after first-line chemotherapy demonstrated significantly prolonged progression-free survival (PFS) and overall survival (OS) in the overall study population of patients with advanced non-small-cell lung cancer (NSCLC).

Methods: After four cycles of platinum-based doublet chemotherapy, patients without progressive disease (PD) were randomised to erlotinib (150 mg/day) or placebo until PD or unacceptable toxicity. In this pre-planned analysis, data are assessed according to response to first-line chemotherapy (complete/partial response [CR/PR] or stable disease [SD]).

Results: Following first-line chemotherapy, 889 non-PD patients were included in the intention-to-treat population (55% SD; 44% CR/PR; <1% unknown response). Erlotinib maintenance therapy significantly prolonged PFS in both the SD (hazard ratio [HR] = 0.68; P < 0.0001) and CR/PR (HR = 0.74; P = 0.0059) groups, while OS was significantly prolonged in the SD group only (HR = 0.72; P = 0.0019). The erlotinib-related OS benefit in the SD group remained significant across subgroups, irrespective of tumour histology and/or EGFR mutation status. The incidence of adverse events was similar in the SD group and the overall population, and erlotinib treatment did not negatively impact quality of life.

Conclusions: Patients with advanced NSCLC and SD following first-line platinum-based doublet chemotherapy derive a significant OS benefit from maintenance erlotinib therapy.

Key words: erlotinib, maintenance, NSCLC, phase III, SATURN, stable disease

Introduction

Standard, first-line platinum-doublet chemotherapy in patients with advanced non-small-cell lung cancer (NSCLC) is usually withdrawn following four to six cycles, due to cumulative toxicity and a lack of increased efficacy with prolonged chemotherapy administration [1]. This leads to a break in therapeutic pressure on the tumour, until second-line therapy is initiated at the time of disease progression.

The oral epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI) erlotinib is an established option for second-line treatment of patients with advanced NSCLC [1–3]. Treatment with erlotinib produces significant survival benefits in a broad patient population and delays the time to the deterioration of key disease symptoms (cough, dyspnoea, and pain), without having a negative impact on patients’ quality of life (QoL) [2, 4]. These benefits are particularly important, given that survival outcomes with erlotinib are similar to those with the approved second-line cytotoxic chemotherapy options docetaxel and pemetrexed [5, 6].

Until recently, treatment guidelines recommended waiting until disease progression before administering later-line systemic anticancer treatments [1, 3]. However, this treatment break meant that a substantial proportion (30%–50%) of patients did not receive any further treatment, often because of rapid disease progression and/or rapid worsening of performance status after the completion of first-line treatment [7–9].
The introduction of maintenance therapy represents a paradigm shift in the treatment of advanced NSCLC and is intended to delay disease progression and extend survival, without adversely affecting patients’ QoL. This approach involves the administration of an active treatment immediately after first-line chemotherapy, thus maintaining the clinical benefit obtained. Maintenance therapy regimens may include the continuation, until disease progression or unacceptable toxicity, of a non-platinum component of first-line therapy, such as gemcitabine or bevacizumab [10–12]. Alternatively, maintenance therapy can involve a ‘switch’ to a new agent, as exemplified by recent trials with erlotinib and pemetrexed [7, 10, 13, 14]. Maintenance therapy with erlotinib or pemetrexed may also be termed ‘early second-line therapy’ since this involves the earlier introduction of approved second-line agents [14].

In the phase III SequentiaI Tarceva® in UnResectable NSCLC (SATURN; BO18192) study, maintenance therapy with erlotinib significantly increased progression-free and overall survival (PFS and OS) versus placebo in both the overall intention-to-treat (ITT) population and in patients with EGFR immunohistochemistry (IHC)-positive tumours [13]. These benefits were observed across clinical and molecular biomarker subgroups, with no impairment in QoL.

Although the benefits of maintenance therapy in NSCLC have now been established, it is likely that some patients may derive greater benefits from this approach than others. Approximately, 70%–80% of patients obtain some clinical benefit from standard, first-line platinum-doublet chemotherapy regimens, with 40%–50% achieving stable disease (SD) as their best response [8, 9, 15–18]. Compared with patients achieving complete or partial tumour response (CR or PR), those with SD after first-line chemotherapy may have substantial residual tumour burden, continuing symptoms, and a worse prognosis [19, 20]. These patients may, therefore, be particularly suitable candidates for maintenance therapy.

We report a prospectively planned analysis of the SATURN study, to evaluate the clinical benefit obtained with maintenance erlotinib, according to response to first-line chemotherapy.

methods

The study design, key inclusion/exclusion criteria, biomarker analyses, assessments, and statistical analysis have been reported separately [13, 21], and are, therefore, only summarised here.

study design and patients

Patients with advanced (stage IIIB/IV) NSCLC, whose disease did not progress following four cycles of standard platinum-doublet chemotherapy, and who had a performance status of zero or one, were randomised (1 : 1) to receive maintenance therapy with either erlotinib 150 mg/day or placebo until unacceptable toxicity or disease progression (PD). The co-primary end points were PFS in the ITT population and PFS in the subpopulation of patients with EGFR protein expression (as assessed by IHC), where at least 10% of tumour cells had membrane staining (IHC-positive). OS was a secondary end point.

The study complied with the Declaration of Helsinki and Good Clinical Practice guidelines, and the protocol was approved at all participating centres by respective ethics committees. All patients provided written informed consent to participate in the study, for collection of tumour samples, and for EGFR IHC testing. Consent for additional molecular analyses was collected separately.

EGFR mutation analyses

Mandatory tumour samples were collected before initiating first-line chemotherapy. Exons 18–21 of the EGFR gene were subjected to PCR assay using nested primers, with mutations confirmed on both strands of at least two PCR products. Samples were classified as activating EGFR mutations positive if the most commonly observed activating mutations were detected (deletions in the region around E746–A750 of exon 19 and/or the L858R point mutation in exon 21) [22].

assessments

Baseline characteristics were assessed at the time of randomisation and included smoking status (never smokers [patients who had smoked <100 cigarettes in their lifetime], former smokers [those who had smoked ≥100 cigarettes but had not smoked within the last year], and current smokers [all remaining patients]). Tumour tissue was collected from all patients at study screening, and tumour assessments were carried out after completion of chemotherapy, then 6-weekly until week 48, and every 12 weeks thereafter or until disease progression. Tumour response was classified by RECIST version 1.0. Adverse events (AEs) were classified according to the National Cancer Institute—Common Terminology Criteria for AEs (NCI–CTCAE) version 3.0, and QoL was evaluated by use of the Functional Assessment of Cancer Therapy–Lung (FACT-L) questionnaire. The Trial Outcome Index (TOI) was defined as the sum of the scores of the physical well being, functional well being, and lung cancer subscale of the FACT-L instrument.

statistical analyses

Time-to-event data were measured from the time of randomisation. Survival outcomes were assessed by use of Kaplan–Meier curves, and hazard ratios (HRs) and 95% confidence intervals (CIs) were determined by Cox regression model. Basic comparisons between the erlotinib and placebo groups were carried out using a two-sided log-rank test. Cox regression analysis of OS was carried out in the ITT population, including response to first-line chemotherapy (CR/PR versus SD) and other baseline characteristics, with stratification factors as covariates. A multiple Cox regression with stepwise selection was also carried out for the ITT population.

results

A total of 1949 patients were screened and received first-line platinum-based doublet chemotherapy. Of the 889 non-PD patients who were subsequently randomised to the ITT population (438 to erlotinib and 451 to placebo), 487 patients (55%) had SD after first-line chemotherapy, 394 patients (44%) had CR/PR, 5 (<1%) patients progressed before randomisation, and the response status of 3 patients (<1%) was unknown. The remaining patients were not randomised to the study due to PD (22%), ineligibility for randomisation (20%), death (8%), and withdrawn consent (5%) (see Cappuzzo et al. [13] for further details of reasons for ineligibility). In the ITT population, baseline clinical and biomarker characteristics were well balanced between the SD and CR/PR groups and also between the treatment arms within these groups (Table 1).

Post-study therapy was documented in approximately two-thirds of patients (in each treatment arm and response
Table 1. Baseline characteristics in patients with CR/PR or SD after completion of first-line chemotherapy

<table>
<thead>
<tr>
<th>Clinical factors</th>
<th>CR/PR (n = 184)</th>
<th>Placebo (n = 210)</th>
<th>SD (n = 252)</th>
<th>Placebo (n = 235)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Female</td>
<td>55 (30)</td>
<td>50 (24)</td>
<td>62 (25)</td>
<td>63 (27)</td>
</tr>
<tr>
<td>Male</td>
<td>129 (70)</td>
<td>160 (76)</td>
<td>190 (75)</td>
<td>172 (73)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>58.7</td>
<td>60.2</td>
<td>60.6</td>
<td>59.2</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>157 (85)</td>
<td>179 (85)</td>
<td>212 (84)</td>
<td>193 (82)</td>
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<tr>
<td>Asian</td>
<td>25 (14)</td>
<td>29 (14)</td>
<td>34 (13)</td>
<td>35 (15)</td>
</tr>
<tr>
<td>Other</td>
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<td>2 (1)</td>
<td>6 (2)</td>
<td>7 (3)</td>
</tr>
<tr>
<td><strong>ECOG PS at BL, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>63 (34)</td>
<td>68 (32)</td>
<td>70 (28)</td>
<td>77 (33)</td>
</tr>
<tr>
<td>1</td>
<td>121 (66)</td>
<td>142 (68)</td>
<td>182 (72)</td>
<td>158 (67)</td>
</tr>
<tr>
<td><strong>Smoking status, n (%)</strong></td>
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<tr>
<td>Current smoker</td>
<td>107 (58)</td>
<td>124 (59)</td>
<td>132 (52)</td>
<td>125 (53)</td>
</tr>
<tr>
<td>Never smoker</td>
<td>29 (16)</td>
<td>27 (13)</td>
<td>47 (19)</td>
<td>48 (20)</td>
</tr>
<tr>
<td>Past smoker</td>
<td>48 (26)</td>
<td>59 (28)</td>
<td>73 (29)</td>
<td>62 (26)</td>
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<tr>
<td><strong>Disease stage, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unresectable IIIB</td>
<td>45 (24)</td>
<td>55 (26)</td>
<td>70 (28)</td>
<td>53 (23)</td>
</tr>
<tr>
<td>IV</td>
<td>139 (76)</td>
<td>155 (74)</td>
<td>182 (72)</td>
<td>182 (77)</td>
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<td><strong>Histology, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>80 (43)</td>
<td>84 (40)</td>
<td>123 (49)</td>
<td>112 (48)</td>
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<tr>
<td>Squamous cell</td>
<td>69 (38)</td>
<td>99 (47)</td>
<td>97 (38)</td>
<td>93 (40)</td>
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<tr>
<td>Other</td>
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<td>27 (13)</td>
<td>32 (13)</td>
<td>30 (13)</td>
</tr>
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<td><strong>Biomarkers</strong></td>
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<td></td>
</tr>
<tr>
<td><strong>EGFR IHC, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>124 (67)</td>
<td>146 (70)</td>
<td>182 (72)</td>
<td>164 (70)</td>
</tr>
<tr>
<td>Negative</td>
<td>26 (14)</td>
<td>25 (12)</td>
<td>36 (14)</td>
<td>34 (14)</td>
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<td>Indeterminate/missing</td>
<td>34 (18)</td>
<td>39 (18)</td>
<td>34 (14)</td>
<td>37 (16)</td>
</tr>
<tr>
<td><strong>EGFR FISH, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>53 (29)</td>
<td>56 (27)</td>
<td>68 (27)</td>
<td>54 (23)</td>
</tr>
<tr>
<td>Negative</td>
<td>43 (23)</td>
<td>56 (27)</td>
<td>84 (33)</td>
<td>71 (30)</td>
</tr>
<tr>
<td>Indeterminate/missing</td>
<td>88 (48)</td>
<td>98 (47)</td>
<td>100 (40)</td>
<td>110 (47)</td>
</tr>
<tr>
<td><strong>EGFR mutation status, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activating</td>
<td>7 (4)</td>
<td>12 (6)</td>
<td>15 (6)</td>
<td>15 (6)</td>
</tr>
<tr>
<td>Resistance</td>
<td>1 (&lt;1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Other mutation</td>
<td>2 (1)</td>
<td>1 (&lt;1)</td>
<td>4 (2)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Wild-type</td>
<td>84 (46)</td>
<td>85 (40)</td>
<td>114 (45)</td>
<td>103 (44)</td>
</tr>
<tr>
<td>Indeterminate/missing</td>
<td>90 (49)</td>
<td>112 (53)</td>
<td>119 (47)</td>
<td>116 (49)</td>
</tr>
<tr>
<td><strong>KRAS mutation status, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classical</td>
<td>19 (10)</td>
<td>22 (10)</td>
<td>30 (12)</td>
<td>19 (8)</td>
</tr>
<tr>
<td>Other mutation</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Wild type</td>
<td>86 (47)</td>
<td>88 (42)</td>
<td>118 (47)</td>
<td>109 (46)</td>
</tr>
<tr>
<td>Indeterminate/missing</td>
<td>79 (43)</td>
<td>100 (48)</td>
<td>104 (41)</td>
<td>106 (45)</td>
</tr>
</tbody>
</table>

Of the 889 patients randomised, 8 patients were not included in this analysis due to progressive disease (n = 5) or due to their response status being recorded as ‘unknown’ (n = 3).

*Other than Indian subcontinent.

*bIncludes pure adenocarcinoma, pure BAC, BAC with focal invasion, and adenocarcinoma with BAC features.

cIn many cases, only small amounts of tissue were available, and so biomarker testing was prioritised in the following order, according to the predefined analysis plan: EGFR IHC, EGFR FISH, KRAS mutation, EGFR mutation. As a result of this, and the different technical failure rates for each analysis, not all biomarkers could be analysed in all patients.

BAC, bronchioloalveolar carcinoma; BL, baseline; CR, complete response; EGFR, epidermal growth factor receptor; ECOG, Eastern Cooperative Oncology Group; IHC, immunohistochemistry; PR, partial response; PS, performance status; SD, stable disease.
to chemotherapy subgroup) and was also generally well balanced (Table 2).

Analysis of PFS according to response to first-line chemotherapy showed similar and significant benefits with maintenance erlotinib, compared with placebo, for both the SD and CR/PR groups (Figure 1A and 1B). The HR for erlotinib benefit was 0.68 in the SD group (95% CI 0.56–0.83; \(P < 0.0001\)) with a median PFS of 12.1 versus 11.3 weeks (2.8 versus 2.6 months), respectively. The HR in the CR/PR group was 0.74 (0.60–0.92; \(P = 0.0059\)) with a median PFS of 12.4 versus 11.1 weeks (2.9 versus 2.6 months), respectively.

In order to assess the prognostic impact of tumour response after first-line chemotherapy, a multiple Cox regression model of OS was carried out, including baseline characteristics and stratification factors as covariates. SD after first-line chemotherapy was a significant negative prognostic factor. For the comparison of CR/PR versus SD, which included baseline characteristics and stratification factors, the HR was 0.79 (95% CI 0.67–0.93; \(P = 0.005\)).

In the SD group, OS was significantly prolonged with maintenance erlotinib, compared with placebo (HR = 0.72 [95% CI 0.59–0.89]; \(P = 0.0019\); median OS 11.9 versus 9.6 months, respectively) (Figure 1C). No significant difference in OS was observed in the CR/PR group (HR = 0.94 [95% CI 0.74–1.20]; \(P = 0.6181\); median OS 12.5 versus 12.0 months in the erlotinib and placebo groups, respectively) (Figure 1D). The OS benefit with erlotinib in the SD group remained significant in a multiple Cox regression analysis including all factors in the model (HR = 0.71 [95% CI 0.58–0.88]; \(P = 0.0019\)).

In the SD group, the 1-year event-free rates for PFS were 5.2% and 1.7% for maintenance erlotinib and placebo, respectively. In the CR/PR group, the corresponding rates were 6.0% and 4.2% for maintenance erlotinib and placebo, respectively.

Table 2. Summary of subsequent therapies in patients with CR/PR or SD after completion of first-line chemotherapy and completion of maintenance phase (patients may have received more than one subsequent therapy)

<table>
<thead>
<tr>
<th></th>
<th>CR/PR</th>
<th>Placebo</th>
<th>SD</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erlotinib</td>
<td>15 (8)</td>
<td>33 (16)</td>
<td>18 (7)</td>
<td>35 (15)</td>
</tr>
<tr>
<td>Placebo</td>
<td>187 (95)</td>
<td>280 (88)</td>
<td>168 (69)</td>
<td>235 (87)</td>
</tr>
<tr>
<td>Docetaxel, n (%)</td>
<td>55 (30)</td>
<td>65 (31)</td>
<td>72 (29)</td>
<td>67 (29)</td>
</tr>
<tr>
<td>Pemetrexed, n (%)</td>
<td>41 (22)</td>
<td>31 (15)</td>
<td>45 (18)</td>
<td>49 (21)</td>
</tr>
<tr>
<td>Vinorelbine, n (%)</td>
<td>15 (8)</td>
<td>22 (10)</td>
<td>17 (7)</td>
<td>20 (9)</td>
</tr>
<tr>
<td>Erlotinib, n (%)</td>
<td>15 (8)</td>
<td>33 (16)</td>
<td>18 (7)</td>
<td>35 (15)</td>
</tr>
<tr>
<td>Gefitinib, n (%)</td>
<td>3 (2)</td>
<td>13 (6)</td>
<td>6 (2)</td>
<td>13 (6)</td>
</tr>
</tbody>
</table>

CR, complete response; PR, partial response; SD, stable disease.

Figure 1. Progression-free survival (PFS) (A, B) and overall survival (OS) (C, D) according to response to prior chemotherapy. CR, complete response; HR, hazard ratio; PR, partial response; SD, stable disease.
7.6% and 3.8%, respectively. For OS, the 1-year event-free rates were 46.8% and 40.9% for maintenance erlotinib and placebo, respectively, in the SD group, and 46.2% and 47.1%, respectively, in the CR/PR group.

**subgroup analyses**

OS improvements were observed across clinical subgroups within the SD group, including both squamous-cell (HR = 0.67 [95% CI 0.48–0.92]; P = 0.0116) and non-squamous-cell histology (HR = 0.76 [95% CI 0.59–1.00]; P = 0.0457) (Figure 2). In the subgroup of patients with SD whose tumours did not have activating EGFR mutations (n = 217), both PFS and OS were significantly prolonged with erlotinib (HR = 0.72 [95% CI 0.54–0.96]; P = 0.0231 and HR = 0.65 [95% CI 0.48–0.87]; P = 0.0041, respectively) (Figure 2). In patients whose tumours had activating EGFR mutations (n = 30), OS was also improved with erlotinib (HR = 0.48), although the 95% CIs were wide (0.14–1.62) due to the small number of patients included in this analysis.

**safety and QoL**

The incidence of AEs was similar in the SD group to that observed in the overall population. Mild or moderate rash and diarrhoea were the most frequently observed erlotinib-related toxic effects (Table 3). QoL and symptom data in this analysis were also similar to the overall study population, with no erlotinib-related QoL impairment. In the SD group, the HRs were time to deterioration of QoL 0.97 (95% CI 0.75–1.26), time to symptom progression 0.92 (95% CI 0.70–1.22), and time to deterioration in the TOI 1.14 (95% CI 0.86–1.50). Corresponding HRs in the CR/PR group were time to deterioration of QoL 0.93 (95% CI 0.69–1.24), time to symptom progression 0.92 (95% CI 0.67–1.26), and time to deterioration in the TOI 0.98 (95% CI 0.71–1.34).

**discussion**

In this pre-planned subgroup analysis of the SATURN study, PFS was significantly prolonged by maintenance erlotinib,
Patients with SD after first-line chemotherapy had significant PFS and OS improvements, regardless of the response to prior chemotherapy. A significant OS benefit was observed in patients who had SD after first-line chemotherapy (HR = 0.72; 2.3-month increase in median OS) compared with those who achieved CR/PR (HR = 0.94). These results were unlikely to have been influenced by underlying differences in the study subgroups, since all groups were well balanced with regard to baseline clinical and biomarker characteristics and post-study treatments. The differences observed in OS outcomes therefore result from the use of maintenance erlotinib and not from differences in prognostic factors or the use of subsequent therapy. This conclusion is supported by preclinical findings showing an association between resistance to cytotoxic drugs and EGFR pathway activation [26, 27], which may lead to increased sensitivity to EGFR inhibitors [27, 28].

Significant and clinically meaningful PFS and OS benefits were observed with maintenance erlotinib in the ITT population of the SATURN study. In this pre-planned analysis, the OS benefit was significant only in patients who had SD after completing first-line chemotherapy: a group of patients who typically have a poor prognosis and who are less likely to receive subsequent therapy. Among the SD group, improved OS was observed across clinical subgroups, including in squamous and non-squamous histologies, and in patients whose tumours did not have activating EGFR mutations. Maintenance therapy with oral erlotinib is therefore an attractive option in these patients, as it provides a significant and clinically meaningful OS benefit, is well tolerated, and does not negatively impact QoL.

Patients with SD after first-line chemotherapy are likely to have tumours that are at least partially resistant to cytotoxic therapy, and so they may benefit more from a change in therapeutic mechanism of action, compared with those who respond to chemotherapy. This is supported by preclinical findings showing an association between resistance to cytotoxic drugs and EGFR pathway activation [26, 27], which may lead to increased sensitivity to EGFR inhibitors [27, 28].

Significant and clinically meaningful PFS and OS benefits were observed with maintenance erlotinib in the ITT population of the SATURN study. In this pre-planned analysis, the OS benefit was significant only in patients who had SD after completing first-line chemotherapy: a group of patients who typically have a poor prognosis and who are less likely to receive subsequent therapy. Among the SD group, improved OS was observed across clinical subgroups, including in squamous and non-squamous histologies, and in patients whose tumours did not have activating EGFR mutations. Maintenance therapy with erlotinib may therefore be considered as a treatment option for patients with NSCLC and SD after first-line platinum-based doublet chemotherapy.

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**funding**

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**disclosure**

Y-LW: Speakers bureau member for Roche, AstraZeneca, Pfizer and Eli Lilly and Company; WB: Speakers bureau member for Roche, AstraZeneca, and Eli Lilly and Company; PG: Roche employee directly involved in the clinical trial which is discussed in this manuscript; FC: Has participated in sponsored conferences and advisory boards for Roche. BC, TC, KP, and GG have declared no conflicts of interest.

**references**