Clinical Evidence for Second- and Third-Line Treatment Options in Advanced Non-Small Cell Lung Cancer

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Abstract
In the U.S. and Europe, the current options for the second- and third-line treatment of advanced non-small cell lung cancer (NSCLC) are cytotoxic drugs and targeted agents. Docetaxel was the first drug approved for second-line treatment after two phase III trials demonstrated its superiority over best supportive care (BSC) alone and single-agent chemotherapy. Pemetrexed was also registered for use as second-line therapy after it was demonstrated to have activity comparable with, and a more favorable toxicity profile than, docetaxel. Erlotinib, an epidermal growth factor receptor inhibitor, is the only biological agent to have been approved in the U.S. and Europe for lung cancer treatment after a study showed its superiority over BSC in recurrent (second-/third-line) NSCLC patients. This review focuses on these drugs, dealing with the results supporting the choice among docetaxel, pemetrexed, and erlotinib in second- and/or third-line treatment. The Oncologist 2008;13(suppl 1):14–20

Introduction
Platinum-based chemotherapy with a third-generation agent (gemcitabine, paclitaxel, docetaxel, or vinorelbine) improves survival and quality of life in patients with advanced non-small cell lung cancer (NSCLC) [1]. Despite these favorable results, most patients receiving front-line chemotherapy experience disease progression. The availability of several new active drugs and trial results in second-line treatment suggests that this strategy can now be considered a standard of care for patients with a good performance status (PS) who are resistant to first-line treatment [1].

Single-Agent Docetaxel Every 3 Weeks
Two phase III trials demonstrated that docetaxel can produce longer survival and better quality of life than with best supportive care (BSC) alone [2] and single-agent chemotherapy [3] (Table 1). In 2000, the results of these studies allowed the registration in the U.S. and Europe of docetaxel (75 mg/m² every 3 weeks) as the first cytotoxic agent for the second-line treatment of NSCLC. In these trials, docetaxel-related toxicity was relevant, despite the significantly better quality of life scores concerning pain control, weight loss, and PS obtained with docetaxel in comparison with the control groups [4]. A phase II randomized trial [5] confirmed that docetaxel at a dose of 75 mg/m² has a more favorable toxicity profile than, and a similar efficacy to, docetaxel at 100 mg/m². The current problem of this treatment remains hematologic toxicity, which, in the registration trials [2, 3], represented the dose-limiting toxicity: neutropenia occurred in 54%–67% of patients and febrile neutropenia...
occurred in 1.8%–8.0%. Moreover, in these studies [2, 3], docetaxel yielded significant nonhematologic toxicities, mainly grade 3–4 asthenia (12%–18%). Nausea and vomiting were also frequent but can generally be well controlled with modern antiemetics.

**SINGLE-AGENT Pemetrexed**

Pemetrexed, a multitargeted antifolate, was shown to be active in recurrent and progressive NSCLC in a large phase II trial [6], and in malignant pleural mesothelioma in a phase III trial [7].

The phase III JMEI trial demonstrated that pemetrexed and standard 3-weekly docetaxel (75 mg/m²) have similar efficacies when used as second-line treatments [8]. Over 1 year, 571 patients resistant to first-line chemotherapy were randomized into this study. Pemetrexed (500 mg/m² i.v.) plus vitamin supplementation was administered every 3 weeks for a median of four cycles, and was shown to be comparable with docetaxel in terms of efficacy: in both arms, the median survival time, response rate, and 1-year survival rate were approximately 8 months, 9%, and 30%, respectively (Table 1).

The most interesting data from that trial are the toxicity results: the safety profile of pemetrexed was significantly better than that of docetaxel. As shown in Table 1, patients treated with docetaxel were more likely to experience grade 3–4 neutropenia \((p < .001)\), febrile neutropenia \((p < .001)\), and infections associated with neutropenia \((3.3\% \text{ versus } 0\%: p = .004)\) than patients treated with pemetrexed. Consequently, fewer patients in the pemetrexed arm required one or more hospitalizations resulting from neutropenic fever \((1.5\% \text{ versus } 13.4\%: p < .001)\), and a more limited use of white blood cell growth factors was observed than in patients who received docetaxel \((2.6\% \text{ versus } 19.2\%: p < .001)\). The superiority of pemetrexed over docetaxel (75 mg/m² every 3 weeks) was also confirmed by noting that all of the other randomized studies using this treatment arm found more neutropenia and febrile neutropenia with docetaxel treatment than with pemetrexed (Fig. 1).

Following these results, at the end of 2004, pemetrexed was registered in the U.S. and Europe for this indication, and was included in the most recent guidelines on the treatment of NSCLC published by the European Society of Medical Oncology, the American Society of Clinical Oncology, and the National Comprehensive Cancer Network [9, 10]. As a result, pemetrexed is recommended for second-line treatment, particularly for patients with a good PS (because, in the phase III registration study, only 11% of patients had a PS score of 2) but also for patients previously treated with platinum-containing first-line chemotherapy who showed neutropenia or some other toxicity, because pemetrexed demonstrated efficacy with low incidences of hematologic and nonhematologic toxicities.

### Table 1. Registration trials for the treatment of recurrent NSCLC: Survival and toxicity

<table>
<thead>
<tr>
<th>Study</th>
<th>Arm</th>
<th>(n) of patients</th>
<th>Response rate (%)</th>
<th>Median survival time (months)</th>
<th>1-Year survival rate (%)</th>
<th>Grade 3–4 neutropenia (%)</th>
<th>Febrile neutropenia (%)</th>
<th>Most frequent grade 3–4 nonhematologic toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAX 317</td>
<td>D100</td>
<td>49</td>
<td>6.3</td>
<td>5.9</td>
<td>37</td>
<td>85.7</td>
<td>22.4</td>
<td>Pulmonary events ((37%))</td>
</tr>
<tr>
<td></td>
<td>D75</td>
<td>55</td>
<td>5.5</td>
<td>7.5</td>
<td>37</td>
<td>67.3</td>
<td>1.8</td>
<td>Pulmonary events ((20%))</td>
</tr>
<tr>
<td></td>
<td>BSC</td>
<td>100</td>
<td>–</td>
<td>4.6</td>
<td>19</td>
<td>–</td>
<td>–</td>
<td>Pulmonary events ((30%))</td>
</tr>
<tr>
<td>TAX 320</td>
<td>D100</td>
<td>125</td>
<td>10.8</td>
<td>5.5</td>
<td>21</td>
<td>77</td>
<td>12</td>
<td>Fatigue ((17%))</td>
</tr>
<tr>
<td></td>
<td>D75</td>
<td>125</td>
<td>6.7</td>
<td>5.7</td>
<td>32</td>
<td>54</td>
<td>8</td>
<td>Fatigue ((12%))</td>
</tr>
<tr>
<td></td>
<td>V/I</td>
<td>123</td>
<td>0.8</td>
<td>5.6</td>
<td>19</td>
<td>31</td>
<td>1</td>
<td>Fatigue ((11%))</td>
</tr>
<tr>
<td>JMEI [8]</td>
<td>Pem</td>
<td>283</td>
<td>9.1</td>
<td>8.3</td>
<td>29.7</td>
<td>5.3</td>
<td>1.9</td>
<td>Fatigue ((5.3%))</td>
</tr>
<tr>
<td></td>
<td>D75</td>
<td>288</td>
<td>8.8</td>
<td>7.9</td>
<td>29.7</td>
<td>40.2</td>
<td>12.7</td>
<td>Fatigue ((5.4%))</td>
</tr>
<tr>
<td>ISEL [21]</td>
<td>G250</td>
<td>1,129</td>
<td>8</td>
<td>5.6</td>
<td>27</td>
<td>0</td>
<td>0</td>
<td>Diarrhea ((3%))</td>
</tr>
<tr>
<td></td>
<td>BSC</td>
<td>563</td>
<td>1</td>
<td>5.1</td>
<td>21</td>
<td>–</td>
<td>–</td>
<td>Asthenia ((3%))</td>
</tr>
<tr>
<td>BR.21 [22]</td>
<td>E150</td>
<td>488</td>
<td>8.9</td>
<td>6.7</td>
<td>31</td>
<td>0</td>
<td>0</td>
<td>Fatigue ((19%))</td>
</tr>
<tr>
<td></td>
<td>BSC</td>
<td>243</td>
<td>0.9</td>
<td>4.7</td>
<td>22</td>
<td>–</td>
<td>–</td>
<td>Fatigue ((23%))</td>
</tr>
</tbody>
</table>

Abbreviations: BSC, best supportive care; D100, docetaxel 100 mg/m² every 3 weeks; D75, docetaxel 75 mg/m² every 3 weeks; E150, erlotinib 150 mg daily; G250, gefitinib 250 mg daily; ISEL, Iressa Survival Evaluation in Lung cancer; NSCLC, non-small cell lung cancer; Pem, pemetrexed 500 mg/m² every 3 weeks; TAX, Taxotere®; V/I, vinorelbine or ifosfamide.
Pemetrexed can also be recommended for elderly patients needing second-line chemotherapy. A recent retrospective analysis [11] of the JMEI trial found that 15% of patients ≥70 years old (n = 86) on pemetrexed had a longer time to progression and a longer median survival time (4.6 and 9.5 months, respectively) than their counterparts treated with docetaxel (2.9 and 7.7 months, respectively; p > .05). Febrile neutropenia was less frequent in the pemetrexed arm (2.5%) than in the docetaxel arm (19%; p = .025). This analysis [11] shows that elderly patients can have as much benefit from second-line cytotoxic chemotherapy with pemetrexed as younger patients, and that this can be achieved with acceptable toxicity rates.

**Single-Agent Weekly Docetaxel**

In order to reduce the hematologic toxicity of docetaxel from that seen with 75 mg/m² given every 3 weeks in second-line non-small cell lung cancer, compared with those obtained with the pemetrexed arm in its registration trial [3].

In a phase II trial, Lilenbaum et al. [12] randomized elderly chemotherapy-naïve patients and/or patients with a PS score of 2 with advanced NSCLC to either 3-weekly docetaxel or a weekly schedule. The primary endpoint was toxicity, and secondary endpoints were response rate, time to progression, and overall survival. Approximately 100 patients were enrolled, with a median age of 75 years; 75% were elderly and 50% had a PS score of 2. Regarding the overall toxicity, the weekly docetaxel regimen demonstrated less neutropenia (0% versus 30%), less febrile neutropenia (0% versus 2%), and less asthenia (23% versus 37%). The median survival times in the weekly docetaxel and 3-weekly docetaxel arms were 6.5 and 2.5 months, respectively. The authors concluded that, in elderly patients and borderline PS patients, weekly docetaxel is preferable to 3-weekly docetaxel in first-line chemotherapy.

In terms of second-line treatment, following a randomized phase II study [13] with safety as a primary endpoint, a weekly docetaxel schedule was compared with the standard schedule in three phase III trials. In a Spanish study [14], more than 250 patients were randomized between 3-weekly and weekly docetaxel (36 mg/m² for 6 weeks every 2 months). The results did not demonstrate significant differences between 3-weekly and weekly docetaxel in either the 1-year survival rate or median survival time (27% versus 22% and 6.6 versus 5.4 months, respectively; p = .076), but an advantage was seen with the weekly schedule in terms of febrile neutropenia (7.8% versus 0.8%; p = .01), although it was associated with significantly higher incidences of anemia (p = .011), diarrhea (p < .05), and grade 3–4 mucositis (p = .032).

In a German study [15], 208 patients were randomized to receive 3-weekly or weekly docetaxel (35 mg/m² for 3 weeks every 28 days), and the primary endpoint was overall survival. A significantly lower rate of hematologic toxicity was recorded for the weekly arm (20.6% versus 4.8% of patients suffered from neutropenia), with a significant difference observed in the median survival time and 1-year survival rate for the two schedules (6.3 versus 9.2 months and 26.9% versus 39.5% in the 3-weekly and weekly treatment groups, respectively; p = .07).

Finally, an Italian study [16] investigated a possible advantage in terms of quality of life using weekly docetaxel (33.3 mg/m² for 6 weeks every 2 months) versus 3-weekly docetaxel in patients with recurrent NSCLC. No difference was found in the global quality-of-life score at 3 weeks. The incidences of pain, cough, and alopecia were significantly lower under the weekly schedule, while the incidence of diarrhea was higher. The response rates and survival times were similar, with median survival times of 29 and

![Figure 1. Main grade 3–4 World Health Organization toxicities measured in randomized trials evaluating docetaxel at a dose of 75 mg/m² given every 3 weeks in second-line non-small cell lung cancer, compared with those obtained with the pemetrexed arm in its registration trial [3].](image-url)
25 weeks in the 3-weekly docetaxel and weekly docetaxel arms, respectively. Because of the sample size in each trial, there was insufficient statistical power to detect clinically relevant differences in overall survival.

Two meta-analyses [17, 18] were recently performed that included these previous randomized trials in order to evaluate whether weekly docetaxel can result in longer survival than with the standard 3-weekly schedule in previously treated advanced NSCLC patients.

In the first meta-analysis [17], a significantly lower incidence of grade 3–4 neutropenia for weekly docetaxel was found (relative risk [RR], 0.22; 95% confidence interval [CI], 0.19–0.42; \( p < .0001 \)). This advantage translates into an absolute benefit of 15%–19%, with nine patients needing to be treated for one to receive a benefit. When considering only the phase III randomized trials (682 patients), overall survival did not differ significantly between the two regimens (RR, 1.01; 95% CI, 0.76–1.42; \( p = .785 \)).

The second meta-analysis, recently published [18], is based on updated individual patient data from 865 patients enrolled in three phase III and two phase II randomized trials. The results show no significant difference in efficacy between weekly docetaxel and 3-weekly docetaxel as second-line treatment in advanced NSCLC patients (median survival time, 26.1 versus 27.4 weeks, respectively; hazard ratio [HR], 1.09; 95% CI, 0.94–1.26; \( p = .245 \)). The risk for febrile neutropenia was significantly lower with the weekly schedule. The authors concluded that weekly docetaxel represents a valid alternative for all patients with NSCLC suitable for second-line chemotherapy, based on a better toxicity profile and no relevant differences in survival.

In conclusion, the results of four randomized trials [13–16] and two meta-analyses [17, 18] demonstrate no difference in survival, although there are some critical issues because of the limited number of patients (about 700) and the different endpoints considered (safety, overall survival, quality of life) that mean that no clear, conclusive definition of the role of a weekly docetaxel schedule can be determined. The use of a weekly docetaxel schedule for relapsed NSCLC patients is not supported by a direct comparison with pemetrexed. If the results of randomized trials using both 3-weekly and weekly docetaxel regimens are compared with the JMEI trial [8], it is possible to conclude that the primary difference in toxicity (neutropenia and febrile neutropenia) would not be significant (Fig. 2). However, nonhematologic toxicities and dose scheduling are more favorable with pemetrexed, and patients may not want to make weekly hospital visits. Moreover, it is important to note that the weekly docetaxel dose and schedule have not been approved by regulatory authorities in the U.S. or Europe.

**Erlotinib in Second-/Third-Line Treatment**

Erlotinib is the only epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) (Table 1) approved in Europe and the U.S. for the treatment of recurrent NSCLC. Gefitinib, another EGFR TKI, was granted accelerated approval in the U.S. on the basis of response rates obtained in two phase II randomized trials [19, 20], but one of the following confirmatory trials (Iressa Survival Evaluation in Lung cancer trial 709), designed with survival as a primary endpoint, failed to meet its primary objective [21]. As a consequence, the marketing application for gefitinib was withdrawn in Europe, and the U.S. indication was subsequently changed in 2005 so that it could be used only in patients who were already receiving and benefiting from it, or in ongoing clinical trials. However, in a similar trial, oral erlotinib at a dose of 150 mg daily demonstrated a survival advantage over BSC alone (median survival times and 1-year survival rates of 6.7 versus 4.7 months and 31% versus 22% for the erlotinib and placebo groups, respectively) [22, 23].

**Selecting a Second-/Third-Line Treatment**

Some issues must be examined before a decision can be made on whether to use pemetrexed, docetaxel, or erlotinib as second-line treatment. First, the lack of data from comparison trials makes the choice difficult, as does the nonhomogene-

![Figure 2](https://example.com/figure2.png)

**Figure 2.** Main grade 3–4 World Health Organization toxicities measured in randomized trials evaluating docetaxel at a dose of 30–40 mg/m² given weekly in second-line non-small cell lung cancer, compared with those obtained with the pemetrexed arm in its registration trial [3].

- The main nonhematologic toxicity was nausea and vomiting.
- First-line treatment only for elderly patients and/or patients with a performance status score of 2.

Abbreviations: FN, febrile neutropenia; N, neutropenia; N-H, nonhematologic toxicity (asthenia).
ity of prognostic characteristics between patients enrolled in the JMEI [8] and BR.21 [22] studies and the lack of important data such as patients’ smoking history in the JMEI study (Table 2), even if the predictive role of a nonsmoking attitude in patients treated with chemotherapy is still unclear. A retrospective study from Singapore [24] observed no differences in response rates between current and former smokers, finding respective median survival times of 18.5 and 13.6 months ($p = .14$). In another study, Nordquist et al. [25] reported a 5-year survival rate of 23% for patients with adenocarcinoma of the lung who had never smoked (never-smokers), compared with 16% for smokers ($p = .004$).

With the use of EGFR TKIs, dramatic differences in response to therapy have been reported between never-smokers and smokers. A multivariate analysis of the BR.21 trial [26] showed that a nonsmoking history was a significant independent predictor of survival, with a median survival time of 12.3 months for never-smokers ($n = 104$) versus 5.5 months for former/current smokers ($n = 358$; HR, 0.54; 95% CI, 0.41–0.71). The same efficacy in never-smokers was found in the Tarceva© Responses in Conjunction with Paclitaxel and Carboplatin (TRIBUTE) study [27], in which, in the subset analysis of never-smokers, the group treated with erlotinib had a median survival time of 22.5 months, compared with only 10.1 months for smokers. All of these results confirm the need to better define the predictive role of a nonsmoking attitude in prospective trials comparing cytotoxic agents with EGFR TKIs.

It is worthwhile emphasizing that the marketing approval for the two chemotherapy agents recommends use “after failure of a previous chemotherapy treatment” in the case of docetaxel and “after previous chemotherapy” for pemetrexed, while the use of erlotinib is advised “after failure of at least one previous chemotherapy regimen.” Strictly conforming to these therapeutic recommendations would mean that the two chemotherapy agents should be used only in second-line treatment, while erlotinib could be used in second- and also subsequent-line therapy.

A retrospective analysis has shown that improvement in survival beyond second-line treatment using chemotherapy is only modest [28]. In the case of erlotinib, benefits in response and survival are similar for those undergoing second- or subsequent-line treatment (median survival times of 6.3 months and 6.8 months for second- and third-line treatments, respectively) [22], so it seems rational to consider second-line treatment with docetaxel or pemetrexed and third-line treatment with erlotinib.

In support of this idea, data derived from a direct comparison of second-line erlotinib treatment with the standard chemotherapy agents pemetrexed and docetaxel in a phase III trial are still not available, and the population treated in the erlotinib registration trial [22, 23] was considered unsuitable for chemotherapy treatment [29]. The option of third-line erlotinib use is also supported by the fact that 50% of patients enrolled in the BR.21 study had already received two lines of chemotherapy, and that this drug, while having

### Table 2. Second-line registered drugs: Clinical prognostic factors and results

<table>
<thead>
<tr>
<th>Study</th>
<th>Arm</th>
<th>n of patients</th>
<th>Median age (years)</th>
<th>Male/ female (%)</th>
<th>Adenocarcinoma (%)</th>
<th>ECOG performance status score 2/3 (%)</th>
<th>≥2 Previous chemotherapy regimens (%)</th>
<th>Response rate (%)</th>
<th>PFS/ TTP (weeks)</th>
<th>Median survival time (months)</th>
<th>1-Year survival rate (%)</th>
<th>Never-smokers (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAX 317 [2]</td>
<td>D75</td>
<td>55</td>
<td>61</td>
<td>66/34</td>
<td>NA</td>
<td>25</td>
<td>20</td>
<td>5.5</td>
<td>12.3</td>
<td>7.5</td>
<td>37</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>BSC</td>
<td>100</td>
<td>61</td>
<td>65/35</td>
<td>NA</td>
<td>25</td>
<td>24</td>
<td>–</td>
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<td>TAX 320 [3]</td>
<td>D75</td>
<td>125</td>
<td>59</td>
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<td>18</td>
<td>26</td>
<td>6.7</td>
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<td>5.7</td>
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<tr>
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<td>60</td>
<td>65/35</td>
<td>52</td>
<td>15</td>
<td>29</td>
<td>0.8</td>
<td>7.9</td>
<td>5.6</td>
<td>19</td>
<td>NA</td>
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<tr>
<td>JMEI [8]</td>
<td>Pem</td>
<td>283</td>
<td>59</td>
<td>69/31</td>
<td>54</td>
<td>11</td>
<td>0</td>
<td>9.1</td>
<td>12.6</td>
<td>8.3</td>
<td>30</td>
<td>NA</td>
</tr>
<tr>
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<td>D75</td>
<td>288</td>
<td>57</td>
<td>75/25</td>
<td>49</td>
<td>12</td>
<td>0</td>
<td>8.8</td>
<td>12.6</td>
<td>7.9</td>
<td>30</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>BSC</td>
<td>243 (121)</td>
<td>59</td>
<td>66/34</td>
<td>49</td>
<td>23/9</td>
<td>50</td>
<td>0.9</td>
<td>8.0</td>
<td>4.7 (5.5) *</td>
<td>22.5 (23) *</td>
<td>17.3</td>
</tr>
</tbody>
</table>

*In the second-line setting only.

Abbreviations: BSC, best supportive care; D75, docetaxel 75 mg/m² every 3 weeks; E150, erlotinib 150 mg daily; NA, not available; Pem, pemetrexed 500 mg/m² every 3 weeks; PFS, progression-free survival; TAX, Taxotere®; TTP, time to progression; V/I, vinorelbine or ifosfamide.
a good tolerability profile without hematologic toxicity, had also shown positive results for both patients with a PS score of 0–1 and those with a PS score of 2–3 (the response rate was 8% for patients with a PS score of 0–1 and 11% for those with a PS score of 2–3; the median survival times were 8.3, 4.3, and 1.9 months in the PS score 0–1, PS score 2, and PS score 3 groups, respectively) [22, 23].

In view of these results, it is reasonable to suggest the use of erlotinib in third-line therapy, where the PS of patients is usually diminished. However, certain factors, either clinical (never-smoker, adenocarcinoma or bronchioloalveolar subtype, female sex, Asian ethnicity) [30, 31] or molecular (immunohistochemical EGFR expression [26], amplification of EGFR measured by fluorescence in situ hybridization [32], or EGFR mutations [33, 34]), have been shown to be predictive of benefits in response and, in some cases, survival when using EGFR inhibitors as second-line treatments. Thus, even though the presence of EGFR mutations did not correlate with longer survival in the BR.21 study [26], the use of EGFR inhibitors could be recommended for second-line therapy instead of chemotherapy.

**Conclusions**

There are some issues that should be considered when choosing between chemotherapy and targeted therapy in the second-line treatment of NSCLC [35]. Pemetrexed is the only drug that has been directly compared in the second-line setting with an active cytotoxic agent, docetaxel, rather than with BSC [8], as is the case for gefitinib [21] and erlotinib [22]. Moreover, the demonstrated superiority of targeted agents over BSC for third-line treatment opens up the debate, in our opinion, about whether second- and third-line treatment options should be evaluated separately. While we are waiting for the results of phase III trials randomizing patients to receive either docetaxel, pemetrexed, or EGFR inhibitors, the comparable activity of pemetrexed, together with its favorable toxicity profile (versus docetaxel), suggests that pemetrexed may be the best option at present for second-line treatment. Erlotinib, therefore, represents the best third-line option in recurrent NSCLC, and could also be used as a second-line treatment in patients who are unsuitable for chemotherapy, or in those with a favorable molecular and/or clinical prognostic profile.

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