New insights in drug development for the non-small cell lung cancer therapy

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1. ABSTRACT
Non-small cell lung cancer (NSCLC) remains a major problem worldwide. Since most patients with NSCLC have advanced disease at diagnosis, to date, chemotherapy, with third-generation platinum-based doublets, represents the standard of care. However, a plateau has been reached with the use of cytotoxic chemotherapy in advanced NSCLC. Advances in the knowledge of tumour biology and mechanisms of oncogenesis have granted the singling out of several molecular targets for NSCLC treatment. To date, erlotinib and gefitinib, epidermal growth factor receptor tyrosine kinase (EGFR-TK) inhibitors have been licensed, erlotinib worldwide and gefitinib in Asian countries, for refractory NSCLC treatment. Currently, bevacizumab, an anti-vascular endothelial growth factor (VEGF) monoclonal antibody, is the only clinically available antiangiogenic agent licensed, in combination with carboplatin plus paclitaxel, for first-line therapy of advanced NSCLC patients in the United States. Several new biologic agents are being evaluated in clinical research and some of them, such as ZD6474, sorafenib and sunitinib, due to the reported preliminary results and the oral administration seem to be promising targeted agents for the treatment of NSCLC. Aim of this review is to discuss about the new insights in targeted agents development for the treatment of NSCLC patients.

2. INTRODUCTION
Non-small-cell lung cancer (NSCLC) - including squamous carcinoma, adenocarcinoma and large cell carcinoma - represents approximately 85% of all lung cancers (1). Surgery is the only curative treatment of NSCLC. Unfortunately, only 20-30% of tumours presents as local disease and could be radically resected (2). Even with complete resection, 5-year survival rates are disappointing (3). These results led to test the role of adjuvant treatment in order to improve this outcome. Recently, the Cancer Care Ontario and the American Society of Clinical Oncology (ASCO) convened a joint expert panel to review the evidence and draft recommendations for adjuvant therapies. Adjuvant cisplatin-based chemotherapy is recommended for routine use in patients with stages II, and IIIA disease. Adjuvant radiation therapy appears detrimental to survival in stage IB and II, while in stage IIIA it is not recommended for routine use because of the lack of prospective, randomized clinical trial data evaluating its efficacy. A clinical trial is underway to determine the advisability of its routine use in this stage (4).

It has been estimated that locally advanced inoperable NSCLC represents about 20% of all lung cancers at diagnosis (1). For patients with unresectable disease, good performance status (PS), and minimal weight
loss, treatment with combined chemoradiotherapy results in better survival than radiotherapy alone. Concurrent chemoradiotherapy seems to be associated with improved survival compared with sequential chemoradiotherapy (5).

Since most patients have advanced disease at diagnosis, chemotherapy is the mainstay of management which has apparently reached a plateau of effectiveness in improving survival of NSCLC patients. Third-generation platinum-based doublets remain the standard of care in patients with good PS (6). In patients with stage IV NSCLC and PS of 2, chemotherapy with single-agent is recommended, but the optimal approach has not been defined (7). Elderly patients, defined as ≥ 70 years old, also derive benefit from chemotherapy. Most elderly patients should receive single agent chemotherapy, but elderly patients with good PS and without significant comorbidities seem to derive a similar benefit from platinum-based doublets compared with their younger counterparts without a prohibitive difference in treatment toxicities (8, 9).

To date, two chemotherapeutic drugs have been licensed for the treatment of recurrent NSCLC. Second-line chemotherapy with docetaxel (10, 11) can prolong survival after platinum-based therapy. Furthermore, pemetrexed has been approved for second-line treatment, since it has been demonstrated that pemetrexed is not inferior in terms of clinical efficacy as compared to docetaxel, but with significantly fewer side effects (12).

Overall, treatment outcome remains poor suggesting a substantial ongoing need for new approaches to improve the results of advanced NSCLC patients. Our increasing understanding of cancer biology has allowed the development of several potential molecular targets for NSCLC treatment essential for the acquisition of cancer phenotype. Better toxicity profile and tolerability than chemotherapy, better target selectivity, availability for chronic treatment, and, in some cases, oral administration have marked these new targeted compounds amongst the most promising investigational drugs in NSCLC patients.

Aim of this review is to discuss about the new insights in targeted agents development for the treatment of NSCLC patients.

3. TARGETED AGENTS: LICENSED DRUGS FOR NSCLC THERAPY

Targeted therapies are designed to interfere with specific aberrant biologic pathways involved in tumorigenesis and a large amount of pre-clinical in vivo and in vitro data have been gathered on the antitumour properties of a number of new biological agents. Several targeted drugs have been introduced in clinical trials in NSCLC and a series of phase III studies have already produced definitive results.

To date, erlotinib and gefitinib, small molecules able to inhibit the epidermal growth factor receptor tyrosine kinase (EGFR-TK) have been licensed, erlotinib worldwide and gefitinib in Asian countries, for refractory NSCLC (13, 14). Currently, bevacizumab, an anti-vascular endothelial growth factor (VEGF) monoclonal antibody, is the only clinically available antiangiogenic agent licensed, in combination with carboplatin plus paclitaxel, for first-line therapy of patients with advanced NSCLC in the United States (US) (15).

3.1. Erlotinib

Erlotinib, an oral daily administered EGFR-TK inhibitor, in combination with chemotherapy for the first-line treatment of NSCLC has been evaluated in two large multicenter, randomized, placebo-controlled clinical trials. Carboplatin plus paclitaxel or cisplatin plus gemcitabine were evaluated in combination with erlotinib in the TRIBUTE (Tarceva Responses in Conjunction with Paclitaxel and Carboplatin) and TALENT (Tarceva Lung Cancer Investigation) trials, respectively (16, 17). In both trials more than 1,000 untreated advanced stage IIIIB/IV NSCLC patients were randomized. In the TRIBUTE trial the median survival time (MST) for patients treated with erlotinib was 10.6 versus 10.5 months for placebo (HR 0.99; p = 0.95, 95% CI, 0.86 -1.16), the objective response rate (OR) was similar between erlotinib and placebo arm (21.5% versus 19.3%, respectively; p = 0.36) (16). Also in the TALENT trial there was no statistically significant difference in any outcome with MST of 43 versus 44.1 weeks, respectively (17). Therefore, there was no clinical benefit in either trial, and currently concurrent use of erlotinib with chemotherapy is not recommended in the first-line treatment of NSCLC (Table 1).

In a phase III randomized trial, named BR.21, erlotinib was compared with placebo in 731 stage III/IV NSCLC patients who had failed first- or second-line chemotherapy. OR was 8.9% in the erlotinib arm and less than 1% in the placebo group (p < 0.001), MST was 6.7 months for those in the erlotinib regimen compared with 4.7 months in the placebo arm (p < 0.001) (13) (Table 2). Erlotinib had a significantly longer median deterioration-times for cough (4.9 versus 3.7 months, p = 0.04); dyspnoea (4.7 versus 2.9 months, p = 0.04); and pain (2.8 versus 1.9 months, p = 0.03). Moreover, 44%, 34%, and 42% of patients receiving erlotinib had improvements in these three symptoms, respectively. This was accompanied by a significant improvement in physical function (31% erlotinib versus 19% placebo, p = 0.01), and global quality of life (QoL) (35% versus 26%, p < 0.0001). Patients with complete (CR) or partial response (PR) were more likely to have improvement in the QoL response than patients with stable (SD) or progressive disease (PD) (p < 0.01) (18).

Based on these results, erlotinib was approved by the US Food & Drug Administration (FDA) in November 2004 and by the European Medicinal Evaluation Agency (EMEA) in October 2005 for the treatment of chemotherapy-resistant advanced NSCLC patients. To date, a phase III randomized trial named TITAN (Tarceva In Treatment of Advanced NSCLC) is ongoing. In this trial patients with refractory NSCLC could receive erlotinib or chemotherapy (docetaxel or pemetrexed) as second- third-line therapy. The main end point is MST and the patients are stratified based on EGFR expression by IHC or FISH or EGFR mutations (19).
New treatment for non-small cell lung cancer

Table 1. Phase III trials with new biological agents in the first-line treatment of advanced non-small-cell lung cancer

<table>
<thead>
<tr>
<th>Regimen</th>
<th>No.pts</th>
<th>OR (%)</th>
<th>PFS (mos)</th>
<th>OS (mos)</th>
<th>OS p-value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CG + Placebo vs CG + Erlotinib 250 mg</td>
<td>365 vs 365</td>
<td>47.2 vs 51.2</td>
<td>6.0 vs 5.8</td>
<td>10.9 vs 9.9</td>
<td>0.04560 vs 0.04560</td>
<td>21</td>
</tr>
<tr>
<td>CG + Gefitinib 250 mg vs CG + Erlotinib 500 mg</td>
<td>345 vs 345</td>
<td>28.7 vs 30.4</td>
<td>5.0 vs 5.3</td>
<td>9.9 vs 9.8</td>
<td>0.6385 vs 0.6385</td>
<td>22</td>
</tr>
<tr>
<td>CP + Placebo vs CP + Erlotinib</td>
<td>540 vs 539</td>
<td>19.3 vs 21.5</td>
<td>4.3 vs 6.0</td>
<td>10.5 vs 10.6</td>
<td>0.05 vs 0.05</td>
<td>17</td>
</tr>
<tr>
<td>CG + Placebo vs CG + Erlotinib</td>
<td>536 vs 533</td>
<td>29.9 vs 31.5</td>
<td>5.4 vs 7.9</td>
<td>10.3 vs 10.0</td>
<td>0.048 vs 0.048</td>
<td>17</td>
</tr>
<tr>
<td>CP + BEV vs CP</td>
<td>434 vs 444</td>
<td>35 vs 15</td>
<td>6.2 vs 4.5</td>
<td>12.3 vs 10.3</td>
<td>0.003 vs 0.003</td>
<td>38</td>
</tr>
<tr>
<td>CG + Bevacizumab 7.5 mg/kg vs CG + Placebo</td>
<td>345 vs 347</td>
<td>34 vs 20</td>
<td>6.7 vs 6.1</td>
<td>NR vs NA</td>
<td>0.61 vs 0.61</td>
<td>40</td>
</tr>
</tbody>
</table>

1Time-to-progression; 2statistically significant; pts = patients; OR = objective response; PFS = progression-free survival; OS = overall survival; mos = months; BEV = bevacizumab; CP = carboplatin plus paclitaxel; CG = cisplatin plus gemcitabine; NA = not applicable; NR = not reported.

Of interest is a phase II study which was conducted to evaluate erlotinib as first-line monotherapy in eighty chemotherapy-naïve uns elected elderly patients (≥ 70 years of age) with stage III/IV disease. There were 8 (10%) PRs, and 33 (41%) patients experienced SD for 2 months or longer. MST was 10.9 months. Considering the reported results, erlotinib should merit further investigation as a first-line therapeutic option in elderly patients (20).

Based on these considerations, the Italian-Canadian trial TORCH (Tarceva OR ChemoTherapy) appears particularly interesting. The design of this phase III randomized, multicenter trial is based on a non-inferiority survival comparison between an experimental strategy including first-line erlotinib, followed at progression by chemotherapy with cisplatin and gemcitabine (PG), and standard arm consisting of first line PG chemotherapy followed at progression by erlotinib. Moreover, this trial will allow evaluating the relationship between molecular predictors, such as EGFR and K-ras mutational status, and erlotinib treatment response. The aim of the TORCH study is to evaluate in a randomized fashion, which is the most appropriate and cost-effective sequential approach of erlotinib and chemotherapy in an unsampled population of metastatic NSCLC patients. An ongoing phase III trial, named SATURN (SequentiAl Tarceva in UnResectable NSCLC), is evaluating the role of erlotinib as maintenance therapy in patients with advanced NSCLC. Non-progressed patients after four cycles of platinum-based chemotherapy are randomized to erlotinib or placebo until PD or unacceptable toxicity. In this trial the patients are stratified according to EGFR IHC or FISH value or EGFR mutations (19).

3.2. Gefitinib

There was no clinical benefit also when gefitinib was combined with chemotherapy as first-line treatment for advanced NSCLC patients in INTACT-1 (cisplatin plus gemcitabine) and INTACT-2 (carboplatin plus paclitaxel) trials (Iressa NSCLC Trial Assessing Combination Therapy) (21, 22). In both these two trials there were three arms comparing chemotherapy plus placebo versus chemotherapy plus gefitinib 250 mg/day versus chemotherapy plus gefitinib 500 mg/day. More than 1,000 patients were randomized per each study. In the INTACT-1 trial there was no difference in efficacy end points between the treatment groups: for the gefitinib 500 mg/day, gefitinib 250 mg/day, and placebo groups, respectively, MSTs were 9.9, 9.9, and 9.9 months (p = 0.4560), median times to progression (MTP) were 5.5, 5.6, and 6.0 months (p = 0.7633), and ORs were 49.7%, 50.3%, and 48% (21). In the INTACT-2 trial there was no difference in any outcome with MSTs of 8.7, 9.8, and 9.9 months for gefitinib 500 mg/day, 250 mg/day, and placebo, respectively (p = 0.64) (22) (Table 1).

Two large phase II trials were conducted with gefitinib monotherapy in patients with advanced NSCLC which progressed after one or more chemotherapy regimens. In these two studies, named IDEAL 1 and 2 (Iressa Dose Evaluation in Advanced Lung cancer), gefitinib, administered at the dose of 250 or 500 mg/day, was demonstrated to be active and well tolerated (23, 24). In May 2003, with an accelerated approval procedure by the FDA, gefitinib was approved as salvage third-line therapy for NSCLC. In a phase III trial named ISEL (Iressa Survival Evaluation in Lung cancer) and comparing gefitinib, at the dose of 250 mg/day, with best supportive care in 1,692 randomized patients with advanced NSCLC who had received one or two prior chemotherapy regimens, a difference between gefitinib and placebo was reported, although this did not reach a statistical significance in the overall population (MST 5.6 versus 5.1 months, p = 0.11)
New treatment for non-small cell lung cancer

Table 2. Phase III trials with new biological agents in the second- third-line treatment of advanced non-small-cell lung cancer

<table>
<thead>
<tr>
<th>Regimen</th>
<th>No.pts</th>
<th>OR (%)</th>
<th>PFS (mos)</th>
<th>OS (mos)</th>
<th>OS p-value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo vs Erlotinib 150 mg daily</td>
<td>243</td>
<td>&lt;1</td>
<td>1.8</td>
<td>4.7</td>
<td>&lt;0.001</td>
<td>13</td>
</tr>
<tr>
<td>Placebo vs Gefitinib 250 mg daily</td>
<td>488</td>
<td>8.9</td>
<td>2.2</td>
<td>6.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo vs Gefitinib 250 mg daily</td>
<td>563</td>
<td>1</td>
<td>2.6</td>
<td>5.1</td>
<td>0.11</td>
<td>14</td>
</tr>
<tr>
<td>Docetaxel 60 mg/m² Q3W vs Gefitinib 250 mg daily</td>
<td>1129</td>
<td>8</td>
<td>3.0</td>
<td>5.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Docetaxel 75 mg/m² Q3W vs Gefitinib 250 mg daily</td>
<td>244</td>
<td>12.8</td>
<td>2.0</td>
<td>14.0</td>
<td>0.914</td>
<td>25</td>
</tr>
<tr>
<td>Docetaxel 75 mg/m² Q3W vs Gefitinib 250 mg daily</td>
<td>245</td>
<td>22.5</td>
<td>2.0</td>
<td>11.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo vs Erlotinib 150 mg daily</td>
<td>733</td>
<td>7.6</td>
<td>2.7</td>
<td>8.0</td>
<td>NS</td>
<td>26</td>
</tr>
<tr>
<td>Gefitinib 250 mg daily</td>
<td>733</td>
<td>9.1</td>
<td>2.2</td>
<td>7.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1Time to treatment failure; pts = patients; OR = objective response; PFS = progression-free survival; OS = overall survival; mos = months; NS = not significant; Q3W = every three weeks.

(14) (Table 2). Based on these results, in June 2005 FDA restricted the use of gefitinib only to patients participating in open clinical trials or continuing previously started treatment. Therefore, gefitinib is still registered only in several Asiatic countries.

The final results of two randomized phase III trials comparing gefitinib to docetaxel in the treatment of recurrent NSCLC patients, were reported. A Japanese trial compared gefitinib at oral dose of 250 mg/day to docetaxel at the dose of 60 mg/m², day 1 intravenously, recycled every 3 weeks. Non-inferiority in MST between gefitinib (11.5 months) and docetaxel (14 months) was not achieved (Hazard Ratio (HR) 1.12; 95.24% Confidence Interval (CI) 0.89, 1.40) according to the predefined criteria (upper CI for HR < 1.25). No statistical evidence of a difference in MST between the two arms was reported (p = 0.33). However, this study suffers from the impact on MST of post-progression therapy, impact which is difficult to assess (25). The other large phase III randomized trial, named INTEREST (Iressa NSCLC Trial Evaluating REsponse and Survival against Taxotere), compared gefitinib 250 mg/day to docetaxel (75 mg/m², day 1 intravenously, recycled every 3 weeks). In a non-inferiority design trial, gefitinib showed similar efficacy as compared to docetaxel (MST of 7.6 and 8 months, respectively), with a lower toxicity profile and inducing a better QoL. These results could support the licensing of gefitinib in refractory NSCLC patients worldwide (26) (Table 2).

Recently, a large phase II randomized trial, the INVITE (Iressa in NSCLC versus Vinorelbine Investigation in The Elderly) study, compared gefitinib to vinorelbine chemotherapy as first-line treatment for advanced NSCLC elderly patients. The study showed similar results but a lower toxicity profile and a better QoL favoring gefitinib (27). These results, and particularly the oral administration revealed both erlotinib and gefitinib as the most promising investigational drugs, even for first-line treatment, in elderly patients with advanced NSCLC.

A randomized trial, named INPAS, comparing gefitinib versus carboplatin plus paclitaxel as first-line therapy of advanced NSCLC never-smoker patients is ongoing in Asiatic countries. This trial evaluates, prospectively, the role of gefitinib, as first-line treatment, in a subgroup of patients resulted, in retrospective analyses, highly sensitive to this drug.

3.3. Predictive factors for sensitivity to EGFR-TK inhibitors

Several clinical and molecular predictive factors for sensitivity to EGFR-TK inhibitors have been evaluated. The clinical benefit with gefitinib therapy appears to be limited to a specific subgroup of patients, namely, women, never smokers, patients with adenocarcinomas, and patients of Asian ethnicity. Smoking status seems to be the strongest predictor, with patients who are never smokers having the greatest likelihood of a clinical response to gefitinib (28). In the ISEL trial, based on a pre-planned subgroup analysis, gefitinib treatment significantly improved survival among never smokers and patients of Asian origin (14).

In contrast, although female gender, adenocarcinoma, Asian ethnicity and a never-smoking history predict for response to erlotinib in the BR.21 study, erlotinib had a significant effect on survival in all subgroups of patients (13). In fact, even if male smokers with squamous-cell carcinoma have not been considered ideal candidates for treatment with erlotinib, in this group MST was significantly improved among patients receiving erlotinib compared with patients with similar characteristics in the placebo arm (p = 0.015). This difference resulted in MST of 5.5 months in the erlotinib arm compared with 3.4 months in the placebo arm (29).

Skin rash is a common adverse effect observed in all clinical trials with EGFR targeting agents. The incidence of rash was higher with erlotinib compared to gefitinib in phase II and III study (30) and may be due to the lower plasma concentration of gefitinib compared with erlotinib when administered at the recommended doses of 250 mg/day and 150 mg/day, respectively. The positive relationship between the development of rash and response and/or survival which has been shown in erlotinib clinical trials makes the occurrence of skin reactions as a potential surrogate marker for anti-EGFR drugs efficacy (31). The relationship between the development of rash and survival is currently being evaluate further and the results should help to guide for the use of EGFR-targeted therapy.

It has been shown that a substantial percentage of tumours with OR to gefitinib or erlotinib harbour somatic mutations in the EGFR gene (32-35). These recently accumulating results suggest that somatic EGFR gene mutations are more frequently detected in NSCLC patients with clinical characteristics reported as predictive of
response to gefitinib or erlotinib, such as adenocarcinoma with bronchiolalveolar features, never-smoking status, female gender and Asian race. No clear association has been described between EGFR expression and sensitivity to EGFR-TK inhibitors. The lack of response in some tumours with high expression of EGFR, suggest that there is no strict correlation between the level of EGFR expression as determined by immunohistochemistry (IHC) and the importance of the EGFR for cancer cell proliferation (36). The degree of expression of EGFR itself is not predictive of the activity of EGFR inhibitors.

Several groups have investigated the potential predictive value of EGFR gene amplification in patients treated with gefitinib or erlotinib. The randomized BR.21 and ISEL studies showed that FISH-positive patients randomized to placebo had a slightly inferior survival compared with FISH-negative patients randomized to placebo (13, 14). In the BR.21 trial, FISH-positive patients (approximately 40%) randomized to receive erlotinib had a significantly superior survival (HR=0.44, p = 0.01), as compared with FISH-positive patients randomized into the placebo arm (HR=0.44, p = 0.01) (13). In the FISH-negative patients, there were no significant difference in survival. Similar results were observed in the ISEL trial in which gefitinib was used (14). Different results come from the INTEREST and INVITE trials (26, 27). Surprisingly, in the INTEREST study gefitinib failed to show a survival advantage versus docetaxel in patients with a high EGFR copy number detected by FISH and, in the INVITE trial, in patients FISH positive for EGFR, vinorelbine induced better outcomes as compared to gefitinib (26, 27). These results raise some doubts about the predictive role of FISH: it could be a prognostic and not a predictive factor? It is important to remark that the main information about the predictive role of clinical and bio-molecular markers comes from retrospective analyses of phase II or phase III trials comparing gefitinib or erlotinib in best supportive care, and that this is the first prospective analysis in a large phase III randomized trial comparing these new biologic agents to chemotherapy. However results from further clinical trials are needed for a better understanding of the predictive role of clinical and bio-molecular markers.

3.4. Bevacizumab

Bevacizumab is an anti-VEGF recombinant humanized monoclonal antibody. Bevacizumab is currently licensed for use in combination with fluorouracil-based chemotherapy for first-line treatment of patients with metastatic colorectal cancer (MCRC) in the US and Europe (37) and in combination with carboplatin plus paclitaxel for first-line therapy of patients with advanced NSCLC in the US (38).

The promising results derived from a phase II trial testing bevacizumab combined with chemotherapy in the treatment of advanced NSCLC (39), carried to a following phase III trial (38). This randomized phase III trial (study E4599) compared the combination of bevacizumab with chemotherapy (carboplatin and paclitaxel) versus chemotherapy alone in the treatment of advanced non-squamous NSCLC (38). Squamous histology was excluded because of risk of grade 5 haemoptysis reported in the previous phase II randomized study. In 878 patients enrolled, a statistically significant advantage in MST (12.3 versus 10.3 months; p = 0.003), progression-free survival (PFS) (6.2 versus 4.5 months; p < 0.001) and OR (35% versus 15%; p < 0.001) was reported in favor of bevacizumab arm. There were 15 treatment-related deaths in bevacizumab group, including 5 from pulmonary hemorrhage (38). This study represents the first evidence of superior efficacy of targeted therapy combined with chemotherapy over chemotherapy alone in the treatment of NSCLC (Table 1).

Recently, the AVAiL (AVAsitan in Lung) trial, a randomized, placebo-controlled phase III study, evaluated bevacizumab in combination with cisplatin plus gemcitabine in advanced non-squamous NSCLC (40). In this trial chemotherapy was compared with chemotherapy plus two different doses of bevacizumab, 7.5 and 15 mg/kg. A total of 1,043 patients were randomized to the three arms. Median PFS, main endpoint of the trial, was 6.1, 6.7, and 6.5 months respectively for chemotherapy alone, chemotherapy plus bevacizumab 7.5 mg/kg and chemotherapy plus bevacizumab 15 mg/kg (p = 0.002 for bevacizumab 7.5 mg/kg; p = 0.03 for bevacizumab 15 mg/kg). The ORs were 20%, 34% and 30%, respectively with a response duration of 4.7, 6.1 and 6.1 months, respectively. Grade ≥ 3 adverse events occurred in 75%, 76% and 81% of the three treatment groups, with treatment-related deaths occurring in 4%, 4% and 5%, respectively. Survival data were not yet mature. This is the second large phase III randomized trial reporting a significant advantage in the main end point for bevacizumab when combined with chemotherapy in the treatment of advanced non-squamous NSCLC (Table 1).

Many doubts exist on the feasibility of bevacizumab in elderly patients, because the toxicity profile of bevacizumab, does not appear particularly suitable to the elderly population, often affected by cardiovascular comorbidities. This topic is particularly relevant if we consider that a great part of lung cancers are diagnosed in patients older than 70 years (41). In the ECOG 4599 trial (38, 42), 224 (26%) out of 850 eligible patients were > 70 years of age (1.6% > 80 years). For the elderly patients, there was a trend towards superior OR (29% versus 17%; p = 0.067) and median PFS (5.9 months versus 4.9 months; p = 0.063) with chemotherapy plus bevacizumab when compared to chemotherapy alone, though there was no difference in MST (chemotherapy plus bevacizumab = 11.3 months; chemotherapy = 12.1 months; p = 0.4). Grade 3-5 toxicities were reported in 87% of elderly patients treated with chemotherapy plus bevacizumab compared to 61% with chemotherapy (p < 0.001), treatment-related death rates were 6.3% versus 1.8%, respectively. In this retrospective analysis, when compared to younger patients, the elderly experienced an higher incidence of toxicities with chemotherapy plus bevacizumab.
4. TARGETED AGENTS: WHAT NEWS?

Other new targeted agents currently undergoing evaluation in preclinical and clinical trials in the treatment of advanced NSCLC include cetuximab (C225), vandetanib (ZD6474), sorafenib, and sunitinib.

4.1. Cetuximab (C225)

Several anti-EGFR monoclonal antibodies are in development for the treatment of NSCLC, and among these cetuximab is the one with the largest amount of clinical data being available on the treatment of advanced NSCLC. Cetuximab is a chimeric (human-murine) monoclonal antibody directed against the extracellular domain of the EGFR which blocks ligand (TGF-alpha, EGF) access to the receptor (43, 44). To date, cetuximab has been licensed for use in combination with irinotecan for the treatment of EGFR-expressing MCRC in patients who are refractory to irinotecan-based chemotherapy or, as single agent, in MCRC patients who are intolerant to irinotecan-based chemotherapy. Cetuximab has been licensed also for use in combination with radiation therapy for the treatment of locally regionally advanced squamous cell carcinoma of the head and neck (SCCHN) or, as single-agent, for the treatment of patients with recurrent or metastatic SCCHN for whom prior platinum-based therapy has failed.

The combination of cetuximab and chemotherapy in advanced NSCLC as first- or second-line treatment has been evaluated in several trials reporting interesting results (45). Among these, a randomised phase II trial studied the combination of cisplatin plus vinorelbine with and without cetuximab in the first-line setting. A total of 86 patients were randomised, 43 per each arm, 90% of which had EGFR-expressing tumours. The cetuximab arm reported an OR of 35% versus 28% of chemotherapy arm alone. Median PFS was 5 and 4.6 months with a MST of 8.3 and 7.3 months, respectively with no statistical significance. The treatment was well tolerated in both arms (46).

A randomized phase III trial study, which compared the combination of cisplatin plus vinorelbine with or without cetuximab in chemotherapy-naïve advanced NSCLC, completed the accrual of the planned 1,125 patients, who had EGFR-expressing disease (47), and recently Merck held a press conference in which communicated a survival advantage for the cetuximab arm.

Recently, a therapeutic strategic phase II randomized trial reported final results. In this trial 242 untreated NSCLC patients were randomly assigned to receive carboplatin plus paclitaxel plus cetuximab or carboplatin plus paclitaxel followed by cetuximab. OR was 34% in the concurrent arm and 31% in the chemotherapy arm only with a SD of 34% and 39%, respectively. PFS was 4 months and MST was 11 months in both arms. Significantly higher neurotoxicity was observed in concurrent arm (15% versus 5.5%), while rash was the only additional toxicity observed in the concurrent arm (11% versus 7%) (48). This strategic approach has been applied also in a phase II randomised trial, performed by our group, named CALC-1 (Cetuximab in Advanced Lung Cancer), and addressed to advanced NSCLC patients unsuitable for combination chemotherapy. This trial completed the planned accrual of 100 patients who have been randomised to receive in the arm 1 the combination of cetuximab and gemcitabine; in the arm 2 gemcitabine followed by cetuximab either as maintenance treatment after 6 cycles of gemcitabine or as second-line treatment after a disease progression during gemcitabine treatment. The primary endpoint is 1-year survival and the final results will be expected soon.

Also for cetuximab, as already reported for erlotinib and gefitinib, clinical and molecular factors were analysed to predict sensitivity or resistance to the drug. The main side effect related to cetuximab treatment is skin rash and there seems to be a correlation between the severity of acneiform rash and the OR and MST. Data from multiple studies with cetuximab, mainly performed in MCRC and SCCHN, show a consistent relationship between rash and response, as well as between rash and survival. The cause of the possible relationship between rash and clinical benefit remains unclear (30). Few data between skin toxicity and clinical benefit from cetuximab-treatment in NSCLC patients are available. These data reported a straight correlation between the grade of rash and OR (46). Therefore, this requires further investigation.

No clear association has emerged between levels of EGFR and response to cetuximab. A retrospective analysis classified the EGFR status of 346 MCRC patients treated with cetuximab monotherapy in undetectable, 1+, 2+, and 3+. EGFR staining did not appear to correlate with increased survival. Conflicting results about EGFR-expression and outcome of NSCLC were reported (45). Anyway, the lack of standardised methods for IHC assessments may provide several potential conflicting data.

The relationship between EGFR mutations and response to cetuximab remains unclear (49). These findings were confirmed also on in vitro NSCLC cell lines with mutant EGFR genotypes on which the effects of gefitinib and cetuximab were examined. The results suggested that EGFR mutations in NSCLC cells are associated with sensitivity to gefitinib but not to cetuximab. Thus, the growth of some NSCLC tumours and cell lines with wild-type EGFR can be inhibited by cetuximab (50). These data suggested that the presence of an EGFR mutation is not a prerequisite for a positive response to cetuximab. Further preclinical and clinical studies are needed to correctly examine the association between EGFR mutations with the activity of cetuximab.

A major correlation between disease response and cetuximab has been found assessing the EGFR copy number by FISH in patients with MCRC. These correlation suggested that patients might be selected for treatment on the basis of EGFR copy number (51). Unfortunately, it is not currently known whether selecting NSCLC patients who are FISH positive for EGFR will derive a higher benefit from cetuximab. Molecular correlative studies on EGFR IHC, FISH, and mutation analysis in NSCLC patients are currently being investigated.
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4.2. Vandetanib (ZD6474)

ZD6474 is an orally bioavailable, aniliquinazoline derivative that has potent inhibitory activity against the VEGFR-2, EGFR-TK, and the ret TK thus, being considered to be a multi-target TKI (52, 53). Several clinical trials have already performed reporting very interesting preliminary results (54).

A phase II randomized trial compared ZD6474 with the EGFR-TKI gefitinib in previously treated IIIb/IV stage NSCLC patients (55). Moreover, the crossover design also allowed to assess the activity of ZD6474 in patients who have failed gefitinib treatment. A total of 168 patients were randomised in part A to receive daily oral doses of either ZD6474 300 mg or gefitinib 250 mg. At PD, after 4 weeks of washout, patients could be optionally switched to the alternative treatment (part B). In part A, ZD6474 produced a statistically significant improvement in PFS than gefitinib (11 weeks versus 8 weeks, respectively; p= 0.025). Disease control > 8 weeks was achieved in 37/83 (45%) patients receiving ZD6474 and in 29/85 (34%) receiving gefitinib. The adverse event profile included skin rash, diarrhoea and asymptomatic QTc prolongation. In part B, disease control > 8 weeks was achieved in 16/37 (43%) patients who switched to ZD6474 (from gefitinib) and in 7/29 (24%) who switched to gefitinib (from ZD6474). MST was not significantly different between patients initially randomised to either ZD6474 or gefitinib (median 6.1 and 7.4 months respectively). This trial achieved its primary efficacy objective, with ZD6474 demonstrating a significant prolongation of PFS versus gefitinib. Despite this, the PFS prolongation did not translate into a MST advantage.

A phase II randomized trial in second-line treatment, enrolled 127 patients with metastatic NSCLC after failure of first-line platinum-based therapy received ZD6474 100 mg plus docetaxel, ZD6474 300 mg plus docetaxel or docetaxel plus placebo. The study met his primary endpoint of PFS prolongation with the addition of ZD6474, with a median PFS of 18.7 weeks for ZD6474 100 mg plus docetaxel (HR versus docetaxel = 0.64; p = 0.074), 17 weeks for ZD6474 300 mg plus docetaxel (HR versus docetaxel = 0.83; p=0.231) and 12 weeks for docetaxel. There was no statistically significant difference in overall survival among the three treatment arms (56). These promising data have led to an ongoing phase III study of ZD6474 plus docetaxel versus docetaxel alone in second-line treatment of NSCLC.

ZD6474 has been tested also in first-line treatment alone or in combination with chemotherapy. Recently, a phase II randomised trial enrolled untreated advanced NSCLC patients to receive ZD6474 or carboplatin plus paclitaxel regimen or this regimen plus ZD6474. ZD6474 has been administered at the oral dose of 300 mg/day. The primary end-point was PFS. A total of 181 patients were randomised, the ZD6474 arm was stopped early after the planned interim PFS analysis met the criterion for discontinuation. Median PFS was 11.6 weeks for ZD6474, 23.1 weeks for chemotherapy and 24 weeks for chemotherapy plus ZD6474, OR was 7%, 18% and 13%, respectively. MST was 11.9 months in chemotherapy alone and 10.2 months in chemotherapy plus ZD6474. There was an higher incidence of grade 3-4 toxicities with ZD6474 plus chemotherapy versus chemotherapy, including rash (7% versus 0%), diarrhoea (8% versus 1%) asymptomatic QTc-related events (8% versus 1%), and hypertension (4% versus 0%) (57).

Considering the oral availability and its favourable toxicity profile, suitable to a peculiar population like NSCLC elderly patients, ZD6474 is among the best candidates for being tested as first-line treatment, in this setting. We are launching a phase II randomised trial, named ZELIG, in which elderly chemotherapy-naïve patients (age ≥ 70 years) with advanced NSCLC will receive gemcitabine plus placebo versus gemcitabine plus ZD6474. The primary endpoint is proportion of patients alive at 1-year. Secondary endpoints are RR, PFS, OS, safety and tolerability.

4.3. Sorafenib

Sorafenib, an orally available agent, is a potent inhibitor of Raf-1 and also active against VEGFR-2, VEGFR-3 and PDGF-receptor (PDGFR)-beta (58). In a phase II trial the efficacy and safety of sorafenib (400 mg twice daily, continuous) was evaluated in patients with relapsed or refractory advanced NSCLC (59). Fifty-two out of 54 enrolled patients received sorafenib. Thirty (59%) out of 51 evaluable patients had SD. Although there were no confirmed PRs, tumour shrinkage was observed in 15 (29%) patients. Patients with SD had a median PFS of 23.7 weeks, while all evaluable patients (n = 51) had a median PFS of 11.9 weeks and MST of 29.3 weeks. The most frequent drug-related adverse events were diarrhoea in 21 (40%), hand-foot skin reaction in 19 (37%) and fatigue in 14 (27%) patients. Grade 3 hypertension occurred in 2 (4%) patients.

Recently, sorafenib has been administered as first-line treatment in advanced NSCLC patients within a phase II trial. A total of 25 patients were enrolled reporting an OR of 12%, a SD of 28% with a median PFS of 2.9 months and a MST of 8.8 months. The treatment was well tolerated registering a grade 3 fatigue in 20%, diarrhoea in 8%, and dyspnoea in 8% of patients. There was one grade 4 pulmonary haemorrhage. Despite the study failed to reach the primary end-point (at least 2 response in the first 20 patients) the reported results suggest that single-agent sorafenib has activity similar to two-drug combinations (60).

4.4. Sunitinib

Sunitinib is a novel oral multitargeted TK inhibitor with activity against VEGFR-1, VEGFR-2, VEGFR-3, c-KIT, PDGFR-alpha and –beta, having both with antitumour and antiangiogenic activities (61, 62).

In a phase II trial the single-agent activity of sunitinib in refractory NSCLC was evaluated (63). Patients received sunitinib at 50 mg/day per os for 4 weeks followed by 2 weeks off treatment (6 weeks considered a cycle). A total of 64 patients were enrolled and 63 patients treated.
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Grade 3-4 toxicities included fatigue/asthenia (21%) and hypertension (5%). Most toxicities were grade 1-2 and included fatigue/asthenia (68%) anorexia (40%). Grade 5 toxicities included pulmonary haemorrhage (2 patients) and cerebral haemorrhage (1 patient). The confirmed PRs were reported in 6 (9.5%) patients among 63 treated patients. SD has been observed in an additional 27 patients (43%). PFS of 11.3 weeks and a MST of 23.9 weeks were reported.

The continuous dosing schedule of sunitinib administered at the dose of 37.5 mg daily in previously treated advanced NSCLC was evaluated in a multicenter phase II study. A total of 47 patients were recruited reporting an OR of 2.1% (1 patient achieved a PR), SD was 19.1%. The median PFS and MST were 12.3 and 37.1 weeks, respectively. Sunitinib was generally well tolerated with grade 3-4 fatigue/asthenia in 17%, and dyspnoea in 8.5% (64).

5. MULTIPLE TARGETED THERAPY

Combining targeted agents that block multiple signaling pathways may reveal a very useful therapeutic approach leading to better outcomes. EGFR and VEGF share common downstream signalling pathways so combining drugs that target these molecules may confer additional clinical benefit. VEGF is also downregulated by EGFR inhibition (65), and a recent study suggested that blockade of VEGF may also inhibit EGFR autocrine signalling (66). Therefore, it is rational to suggest that dual blockade of these molecular targets may produce additive and even synergistic cytostatic effects. Several preclinical and clinical trials have already produced the preliminary results in the treatment of advanced NSCLC.

Recently, a phase II, multicenter, randomised clinical trial evaluated the efficacy and safety of bevacizumab in combination with either chemotherapy (docetaxel or pemetrexed) or erlotinib compared with chemotherapy alone for treatment of recurrent or refractory NSCLC with PFS as primary endpoint. A total of 120 patients were randomised reporting the following results: OR was 17.9%, 12.5%, and 12.2% in bevacizumab plus erlotinib arm, chemotherapy plus bevacizumab arm, and chemotherapy alone, respectively; PFS was 4.4, 4.8, and 3.0 with a MST of 13.7, 12.6, and 8.6, respectively. Fewer patients (13%) in the bevacizumab-erlotinib arm discontinued treatment as a result of adverse events than in the chemotherapy alone (24%) or bevacizumab-chemotherapy (28%) arms. These trial results support examination of the combination of bevacizumab and erlotinib in a phase III trial. If confirmed in a phase III setting, this combination may represent an alternative to chemotherapy (67). A phase III trial comparing the combination of erlotinib plus bevacizumab or placebo in second-line setting, named BETA Lung (Bevacizumab plus Tarceva), is ongoing. These two trial could define the effective role of this combination in second-line treatment of advanced NSCLC patients (19).

The combination of erlotinib and bevacizumab has been evaluated also as first-line treatment within a phase II study. Patients with advanced non-squamous NSCLC who had received no prior chemotherapy were treated with erlotinib plus bevacizumab until PD or unacceptable toxicity. Among 46 patients enrolled into the trial, an OR of 20% with a MST of 7.9 months was reported. Median PFS was 5.7 months. The most common treatment-related adverse events were skin rash (64% of patients) and diarrhoea (53%). No treatment-related deaths were observed (68).

Two phase I trials were conducted to assess the safety and efficacy of sorafenib in combination with either gefitinib (69) or erlotinib (70). In both trials the employed drugs could be administered at their full single-agent recommended dose, with acceptable toxicity.

A phase II randomised trial, named GEST, is ongoing. In this trial elderly and PS 2 patients with advanced NSCLC will be randomised to receive either gemcitabine plus sorafenib or erlotinib plus sorafenib. The primary endpoint is 1-year survival and secondary objectives are activity, toxicity and MST. The combination of erlotinib plus sorafenib could be of interest not only for the possibility to inhibit many targets but also to develop totally oral active and well tolerated treatments in special fragile populations unsuitable for a platinum-based chemotherapy (71).

6. PERSPECTIVE

Many new biologic agents reported interesting results in the therapy of advanced NSCLC but only two of them, erlotinib and bevacizumab, are currently licensed for the treatment of metastatic NSCLC.

Erlotinib is the first oral EGFR-TK inhibitor showing a benefit in the treatment of recurrent NSCLC. However, it is of importance to define the patient population who will derive the most benefit from erlotinib treatment by clarifying the relationship between clinical and/or molecular predictive factors and outcomes. A series of studies is planned to contribute to our understanding of the role of erlotinib in NSCLC treatment. Major areas of clinical research are: the assessment of erlotinib in the adjuvant treatment, combined to chemotherapy and/or radiotherapy in locally advanced disease, in the first line therapy of advanced disease, such as TORCH trial, and in combination and/or sequence with cytotoxic treatments and/or other molecular target agents. Bevacizumab is, at the moment, the first targeted agent that has demonstrated, in combination with chemotherapy, to improve the outcomes of chemotherapy alone in the treatment of advanced NSCLC. But, the fact that the administration of bevacizumab is restricted to patients with non-squamous histotype, no brain metastases, and without main cardiovascular comorbidities, limits its use in a larger population. Many angiogenetic agents without these limitations are being evaluated in clinical research and some of them, such as ZD6474, sorafenib and sunitinib, due to their first evidences of antitumor activity, good toxicity profile, and oral administration seem to be promising targeted agents for the treatment of NSCLC.
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Anyway, based on these results, bevacizumab is being evaluated also in early stages NSCLC in the adjuvant setting and in combination with chemotherapy and radiotherapy into the treatment of locally advanced disease with several phase I/II trials ongoing (72).

As laboratory investigations continue to elucidate mechanisms that contribute to the malignant phenotype, new molecular targets for anticancer therapy emerge, and consequently new targeted drugs are proposed and developed. Several biologic agents have been introduced in the treatment of NSCLC, the majority of which are still in phase I, II or III of clinical evaluation. Still few data are available with these new agents in the treatment of NSCLC patients, but a number of clinical trials are under way or planned to start in the near future.

The first generation of clinical trials, currently still underway, on targeted therapies include single-agent treatment or combined with cytotoxic chemotherapy. NSCLC is a malignancy with a great heterogeneity of molecular events, thus it is unlikely that only one downstream signalling pathway is determining the oncogenic features of all the cancers. The complexity of the signalling process driving to cancer cell proliferation and to the acquisition of a neoplastic phenotype supports the necessity to interfere at different stages to avoid an escape of potential resistance mechanisms. This could be performed through two main approaches: new agents targeting multiple receptor TK, or combination of new biologic agents. This latter approach, although in a preliminary phase, represents the second generation of studies in this field.

7. REFERENCES

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