Recent issues in first-line treatment of advanced non-small-cell lung cancer: Results of an International Expert Panel Meeting of the Italian Association of Thoracic Oncology

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1. Introduction

Since a landmark meta-analysis demonstrated a significant, although clinically modest, improvement in overall survival compared to best supportive care [1], platinum-based chemotherapy has been considered the standard first-line treatment for good performance status patients with advanced non-small-cell lung cancer (NSCLC). A number of different randomized trials have demonstrated similar results for several commonly used platinum-based doublets, combining cisplatin or carboplatin with a “third-generation” drug (gemcitabine, vinorelbine, paclitaxel, docetaxel) [2–4].

In order to demonstrate differences in efficacy between drugs to be combined with the platinum analogue, several meta-analyses have been performed [5–7]. In a meta-analysis comparing the efficacy of gemcitabine plus platinum with other platinum-containing

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regimens in advanced NSCLC, a significant reduction in overall mortality in favor of gemcitabine-containing regimens was described, although this difference was not significant when comparison was limited to regimens of platinum plus a third-generation drug (but is still significant for progression-free survival) [5]. In another meta-analysis, pooling the data of seven trials comparing docetaxel-based with vinca alkaloid-based chemotherapy as first-line treatment of advanced NSCLC, docetaxel was superior to vinca alkaloid-based regimens in terms of overall survival and toxicity [6]. Finally, the most recent meta-analysis attempted to assess the relative impact of different third-generation drugs on the activity of first-line chemotherapy by considering both response and progressive disease rates as outcome measures of 45 randomized trials [7]. The odds of obtaining an objective response to treatment were similar across the diverse regimens. Gemcitabine-based chemotherapy was associated with a lower risk for immediate progression, whereas patients receiving paclitaxel showed the highest risk of early progressive disease. These data seem to suggest modest superiority of gemcitabine- or docetaxel-containing regimens over other third-generation doublets. However, the common feeling was that a plateau has been reached with chemotherapy in the treatment of advanced NSCLC, and the choice was generally based on considerations about toxicity and convenience of administration of different regimens.

Finally, after many years without clinically significant advances in this setting, the selection of optimal treatment in 2009 appears no longer to be limited to the mere comparison of the advantages and limitations of platinum-based doublets. Some randomized trials, conducted with new agents, recently have produced positive results in the first-line setting. These new agents have been evaluated in combination with platinum-based chemotherapy (bevacizumab, cetuximab), as a first-line alternative to chemotherapy (gefitinib) or as maintenance treatment for patients completing the planned number of cycles of chemotherapy without progressive disease (pemetrexed, docetaxel, erlotinib). Furthermore, data from recent trials conducted with pemetrexed-based treatment consistently suggest a significant interaction between treatment efficacy and tumor histology. Significant interaction has been shown also between the efficacy of epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) and the presence of sensitizing EGFR mutations in the tumor. This supports the concept that treatment choice should be no longer the same for all the NSCLCs and should take into account tumor histology subtyping and molecular profiling.

With the aims of reviewing strengths and limitations of the recent evidence with respect to the first-line treatment of advanced NSCLC, discussing the implications for clinical practice and suggesting priorities for clinical research in this field, the Italian Association of Thoracic Oncology (AIOIT, Associazione Italiana di Oncologia Toracica) organized an International Expert Panel Meeting, that took place in Sperlonga, Italy, in May 2009. Results of that meeting are presented in this paper.

2. Methods

2.1. Search strategy and selection criteria

The International Experts Panel Meeting on “First-line treatment of advanced NSCLC”, organized by AIOIT, was held in Sperlonga, Italy on 7 May 2009.

Ten oncologists (four from Italy, one each from Austria, Canada, France, Germany, Spain and USA) formed the scientific panel of the Meeting. Members of the panel were selected among the experts involved in the principal clinical trials – completed or ongoing – on first-line treatment of advanced NSCLC.

Published data useful for panel discussion regarding the evidence produced with new drugs in first-line treatment of advanced NSCLC were identified by a PubMed search performed by each of the panelists on the topic assigned. Only papers written in English were considered. Abstracts presented at the American Society of Clinical Oncology (ASCO) meetings between 2004 and 2008 were also searched (this search has been subsequently updated for the manuscript with the proceedings of 2009 ASCO meeting). Also abstracts presented in the same years at IASLC/WCLC (International Association for the Study of Lung Cancer/World Conference on Lung Cancer), updated for the manuscript with the proceedings of 2009 Conference, ESMO (European Society of Medical Oncology) and ECCO (European Conference of Clinical Oncology), updated with the proceedings of the 2009 ECCO/ESMO meeting, were searched. Relevant references from selected articles were also included and other articles were selected from the personal collections of the panelists.

2.2. Main limitations

Several important topics were excluded from the meeting agenda, because they had been addressed previously in existing guidelines and no relevant results have been recently produced. In particular, the following topics were not discussed during the meeting and are not covered in this paper: (i) choice between platinum analogue; (ii) number of drugs to be used in first-line treatment: single-agent vs. two-drug vs. three-drug combinations; (iii) role of combinations without platinum; (iv) treatment of special patient populations (elderly, unfit patients); and (v) dose and schedule issues. Readers are referred to existing guidelines for a discussion of these topics [8–10].

When discussing the recent data that would potentially result in changes in clinical practice, the panelists considered that several limitations may significantly affect their strength: (i) some data remain unpublished in peer-reviewed journals, and the discussion was necessarily based on meeting presentations; (ii) some evidence is based on subgroup analyses, that should always be interpreted with caution, because of the risk of false positive or false negative results due to multiple, underpowered comparisons; (iii) the panelists agreed that the strongest evidence should remain prolongation of overall survival (OS), while some of evidence in this review is based on surrogate endpoints, such as response rate and progression-free survival (PFS).

3. Results

3.1. Recent results obtained with new agents given as first-line induction therapy

3.1.1. Bevacizumab in addition to first-line chemotherapy

Bevacizumab is a monoclonal antibody directed against vascular endothelial growth factor (VEGF). Evidence about its efficacy in combination with first-line platinum-based doublet chemotherapy comes from two large randomized, phase III trials (Table 1), ECOG 4599, which was conducted in the USA [11] and AVAIL, conducted mainly in Europe, Australia, and Canada [12]. In both trials, the anti-VEGF antibody was administered concurrently with first-line chemotherapy. Subsequently, for patients who completed the planned six cycles of chemotherapy without disease progression, bevacizumab was continued as single-agent treatment until disease progression or unacceptable toxicity. In the early clinical trials previously conducted in advanced NSCLC, the addition of bevacizumab to chemotherapy was associated with a significantly increased risk of bleeding [13], with serious hemorrhagic events seen more frequently among patients with squamous cell carcinoma. However,
it was not completely clear whether the increased bleeding risk was due to histology alone or due to tumor location adjacent to major blood vessels, or whether it might be a consequence of tumor necrosis and cavitation that occurred in response to treatment. As a result of these observations, the phase III trials were both conducted in a selected population, limiting eligibility to patients with non-squamous histology and excluding patients with major risk factors for bleeding: presence of metastases in the central nervous system, history of gross hemoptysis, history of documented hemorrhagic diathesis or coagulopathy; therapeutic anticoagulation; regular use of aspirin, non-steroidal anti-inflammatory agents, or other agents known to inhibit platelet function [11,12]. In the AVAiL trial, tumors invading or abutting major blood vessels also were excluded, considering that location might be associated with a major risk of bleeding, independently from tumor histology [12]. A retrospective evaluation of the clinical and radiographic risk factors associated with severe pulmonary hemorrhage in patients receiving carboplatin and paclitaxel plus bevacizumab as first-line treatment for advanced NSCLC showed that baseline tumor cavitation, and not tumor location, was the only potential risk factor [14].

The ECOG 4599 trial tested the addition of bevacizumab to carboplatin plus paclitaxel [11]. In the experimental arm, bevacizumab was administered at the dose of 15 mg/kg every 3 weeks. In the selected population of 878 patients, the addition of bevacizumab to chemotherapy produced a statistically significant and clinically relevant improvement in OS (median 12.3 months vs. 10.3 months, hazard ratio [HR] 0.79, 95% confidence intervals [CI] 0.67–0.92, \( P < 0.001 \)). Patients receiving bevacizumab also showed a significant improvement in PFS (HR 0.66; \( P < 0.001 \)), and in objective response rates (35 vs. 15%, \( P < 0.001 \)). Treatment with bevacizumab was well tolerated in the majority of patients, but despite the strict exclusion criteria, was still associated with increased risk of clinically significant bleeding (4.4 vs. 0.7%, \( P < 0.001 \)). Furthermore, there were 15 treatment-related deaths in the group receiving chemotherapy plus bevacizumab, including five cases from pulmonary hemorrhage.

The AVAiL trial was designed to replicate the results obtained in ECOG 4599, testing the addition of bevacizumab to cisplatin plus gemcitabine, a chemotherapy regimen widely used outside the USA [12]. Eligible patients were randomized to receive (a) chemotherapy plus placebo (347 patients), (b) chemotherapy plus bevacizumab 7.5 mg/kg (345 patients), and (c) chemotherapy plus bevacizumab 15 mg/kg (351 patients). The study was initially designed with OS as primary endpoint, but this was amended to PFS. This choice was motivated in order to obtain results more rapidly, and to avoid the risk that the primary comparison could have been jeopardized by the impact of second-line treatments. There was no protocol-specified crossover to bevacizumab for patients assigned to placebo. The improvement in PFS for the two arms treated with bevacizumab compared to the placebo group was statistically significant, although small in absolute terms. Median PFS was 6.1, 6.7, and 6.5 months in the chemotherapy-alone, chemotherapy plus bevacizumab 7.5 mg/kg, and chemotherapy plus bevacizumab 15 mg/kg arms, respectively. HRs of progression compared to control were 0.75 (CI 0.62–0.91) and 0.82 (CI 0.68–0.98) for the lower and higher doses of bevacizumab, respectively. No differences in OS were apparent at the analysis of this trial presented at the 2008 ESMO meeting [15], and unfortunately no OS results are included in the study final publication [12]. Treatment with bevacizumab was associated with acceptable toxicity, low rates of clinically relevant bleeding, and pulmonary hemorrhage. In conclusion, bevacizumab 15 mg/kg has shown a significant improvement in overall survival when added to carboplatin plus paclitaxel and a statistically significant prolongation in PFS when

### Table 1

<table>
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<tbody>
<tr>
<td><strong>Control arm</strong></td>
<td><strong>Experimental arm</strong></td>
</tr>
<tr>
<td>Carboplatin AUC 6 + paclitaxel 200 mg/m², day 1 every 3 weeks for up to six cycles</td>
<td>Carboplatin AUC 6 + paclitaxel 200 mg/m², day 1 every 3 weeks for 6 cycles + bevacizumab 15 mg/kg, day 1 every 3 weeks until disease progression or unacceptable toxicity</td>
</tr>
<tr>
<td><strong>Number of patients assigned to control</strong></td>
<td><strong>Number of patients assigned to bevacizumab</strong></td>
</tr>
<tr>
<td>No upper limit</td>
<td>No upper limit</td>
</tr>
<tr>
<td><strong>Primary endpoint</strong></td>
<td><strong>Performance status</strong></td>
</tr>
<tr>
<td>Overall survival</td>
<td>ECOG 0–1</td>
</tr>
<tr>
<td><strong>Eligibility criteria</strong></td>
<td><strong>Histology</strong></td>
</tr>
<tr>
<td>Age</td>
<td>No predominantly squamous cell</td>
</tr>
<tr>
<td><strong>Main exclusion criteria</strong></td>
<td><strong>Main results</strong></td>
</tr>
<tr>
<td>Hemoptysis, central nervous system metastases, documented hemorrhagic diathesis or coagulopathy, therapeutic anticoagulation, regular use of aspirin or NSAID, medically uncontrolled hypertension</td>
<td>Overall survival</td>
</tr>
<tr>
<td>Median in bevacizumab arm</td>
<td>12.3 months</td>
</tr>
<tr>
<td>Median in control arm</td>
<td>10.3 months</td>
</tr>
<tr>
<td>0.79 (0.67–0.92)</td>
<td>Hazard ratio (95% CI) 0.66 (0.57–0.77)</td>
</tr>
<tr>
<td><strong>P (log–rank test)</strong></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0.003</td>
<td>Hazard ratio (95% CI) 0.79 (0.67–0.92)</td>
</tr>
<tr>
<td>7.5 mg/kg: 7.5 mg/kg: 15 mg/kg: 13.6 months; 13.1 months; 13.4 months</td>
<td>7.5 mg/kg: 6.7 months; 15 mg/kg: 6.5 months</td>
</tr>
<tr>
<td>7.5 mg/kg: 0.93 (0.78–1.11); 15 mg/kg: 1.03 (0.86–1.23)</td>
<td>6.1 months</td>
</tr>
<tr>
<td>7.5 mg/kg: 0.42; 15 mg/kg: 0.76</td>
<td>7.5 mg/kg: 0.75 (0.62–0.91); 15 mg/kg vs. placebo: 0.82 (0.68–0.98)</td>
</tr>
<tr>
<td>7.5 mg/kg: 0.93 (0.78–1.11); 15 mg/kg: 1.03 (0.86–1.23)</td>
<td>7.5 mg/kg: vs. placebo: 0.003; 15 mg/kg vs. placebo: 0.03</td>
</tr>
</tbody>
</table>

AUC, area under the concentration–time curve (mg per ml per minute); CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; NSAID, non-steroidal anti-inflammatory drug; NSCLC, non-small-cell lung cancer.
added to cisplatin plus gemcitabine at doses of 7.5 or 15 mg/kg. There are several relevant issues about the interpretation of these results. First, when added to cisplatin and gemcitabine, bevacizumab demonstrated only modest benefit in a surrogate endpoint (PFS), without prolongation of OS. Information from retrospective analysis and large observational studies has confirmed the safety profile of first-line bevacizumab with a wide range of chemotherapy partners [16], but whether its efficacy is comparable when combined with different regimens is still uncertain. Second, bevacizumab was administered as single agent after completion of chemotherapy, based on the rationale that withdrawal of anti-VEGF treatment might be associated with rapid vascular regrowth, but randomized data elucidating the role of bevacizumab as maintenance treatment are still lacking. Third, the identification of predictive factors of efficacy would be relevant for the optimal use of the drug, but to date there no validated biomarkers that predict response to VEGF inhibitors. Some interesting data suggest that treatment-related hypertension could be a surrogate marker of efficacy of bevacizumab [17], but this observation needs further confirmation in future studies.

Both the U.S. Food and Drug Administration (FDA) (October 2006) and European Medicines Agency (EMEA) (August 2007) approved bevacizumab for first-line treatment of advanced, non-squamous NSCLC, in combination with carboplatin plus paclitaxel or any platinum-based chemotherapy, respectively (see Table 2).

The expert panel recommended caution in patient selection for treatment with bevacizumab. Addition of bevacizumab to first-line chemotherapy should be considered among treatment options only in patients consistent with the eligibility criteria of the two randomized trials (see Table 1).

The presence of brain metastases was an exclusion criterion in randomized trials, but treatment with bevacizumab has been shown to be safe in phase II trials of NSCLC patients with treated brain metastases [18], and these are currently no longer considered an absolute contraindication to its administration. Caution should be adopted when treating elderly patients with bevacizumab. Notably, in the subgroup analysis of fit elderly patients enrolled in ECOG 4599, the addition of bevacizumab to carboplatin plus paclitaxel was associated with a higher degree of toxicity [19]. Grade 3–5 toxicities occurred in 87% of elderly patients receiving bevacizumab compared to 61% of those assigned to the control arm. In particular, elderly patients had a higher incidence of severe neutropenia, bleeding, and proteinuria compared with younger patients.

### 3.1.2. Cetuximab in addition to first-line chemotherapy

Cetuximab is a monoclonal antibody directed against the EGFR. The FLEX randomized phase III study aimed to assess the efficacy of the addition of cetuximab to first-line chemotherapy (see Table 3) [20]. Eligibility of patients was limited to cases with tumors expressing EGFR protein assessed by immunohistochemistry (IHC). The primary endpoint of the trial was OS. Eligible patients were randomly assigned to cisplatin plus vinorelbine alone (n = 568) or with cetuximab (n = 557). Patients in the experimental arm received cetuximab concomitantly with chemotherapy, and as maintenance treatment until disease progression or unacceptable toxicity for those completing the planned six cycles of chemotherapy. Study results showed a small but statistically significant benefit for cetuximab in OS (median 11.3 vs. 10.1 months; HR 0.871, CI 0.762–0.996, P = 0.044). Cetuximab was associated with an increase in objective response rate (36% vs. 29%, P = 0.010), without a difference in PFS (median 4.8 months in both groups, HR 0.943, 95% CI 0.825–1.077). Addition of cetuximab to chemotherapy was associated with higher rates of grade 3 acne-like skin rash (10% vs. <1%), severe diarrhea (5% vs. 2%), severe infusion-related reactions (4% vs. <1%), febrile neutropenia (22 vs. 15%), without a significant difference in treatment-related deaths. Subgroup analysis showed no significant interaction between treatment efficacy and patient characteristics (age, sex, performance status, tumor histology, tumor stage, history of smoking). Only the interaction between the treatment and the ethnic origin was significant, showing a trend of greater efficacy for the addition of cetuximab in Caucasian patients compared to Asian or other origin. Following the consistent results produced in patients with colorectal cancer, showing that the efficacy of cetuximab is limited to patients with wild-type KRAS, KRAS mutation status was analyzed in archived tumor samples of 554 out of the 1125 patients enrolled in the FLEX study [21]. The comparison of treatment efficacy in patients groups according to KRAS mutation status did not show relevant differences in terms of either OS or PFS. Similarly, no predictive role was shown for EGFR gene copy number. Interestingly, the best predictor of clinical benefit for the addition of cetuximab to chemotherapy appeared to be treatment-related early acne-like skin rash. All patients assigned to the experimental arm who were alive after the first 3 weeks were included in a landmark analysis evaluating the relationship between early-onset skin rash and survival outcome [21]. Early-onset acne-like rash of any grade was associated with better outcome: patients treated with cetuximab who developed rash of any severity had a significantly higher incidence of OS than those who did not.

### Table 2

<table>
<thead>
<tr>
<th>Drug</th>
<th>U.S. FDA</th>
<th>EMEA</th>
</tr>
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<tbody>
<tr>
<td>Pemetrexed</td>
<td>October 2008: approved in combination with cisplatin for non-squamous NSCLC</td>
<td>April 2008: approved in combination with cisplatin for patients with other than predominantly squamous NSCLC</td>
</tr>
<tr>
<td></td>
<td>July 2009: approved as maintenance therapy for non-squamous NSCLC patients, in whom disease has not progressed after four cycles of platinum-based first-line chemotherapy</td>
<td>July 2009: approved as monotherapy for maintenance treatment of patients with other than predominantly squamous cell histology in locally advanced or metastatic NSCLC, whose disease has not progressed immediately following platinum-based chemotherapy</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>October 2006: approved, at the dose of 15 mg/kg, in combination with carboplatin and paclitaxel for non-squamous NSCLC</td>
<td>August 2007: approved, at the dose of 7.5 or 15 mg/kg, in combination with platinum-based chemotherapy, for other than predominantly squamous cell NSCLC</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>December 2008: application submitted for the first-line treatment of patients with advanced NSCLC in combination with platinum-based chemotherapy (cisplatin/vinorelbine)</td>
<td>September 2008: negative opinion, recommending the refusal of an extension of indication to add the treatment of NSCLC to the marketing authorization</td>
</tr>
<tr>
<td></td>
<td>January 2009: application withdrawn because of issues related to the drug formulation; expected to be resubmitted in the second half of 2009</td>
<td>November 2009: negative opinion confirmed</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>March 2009: application for use as a first-line maintenance treatment</td>
<td>March 2009: application for use as a first-line maintenance treatment</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>-</td>
<td>August 2009: overall survival data of the SATURN trial added to the application</td>
</tr>
</tbody>
</table>

Information updated as of 20 November 2009. EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; TK, tyrosine kinase.
testing and deserves further investigation. Second, considering the 
tive factors would be essential for the optimal use of the drug, but 
of patients. In the latter hypothesis, the identification of predic-
patients or could be driven by a relevant effect limited to a subgroup 
vival (1.2 months of difference in median OS). This limited benefit 
in the risk of death) and in terms of absolute prolongation of sur-
rone (1.3 months of difference in median OS; HR 0.63, CI 0.52–0.77, 
A second randomized trial (BMS 099) tested the addition of 
cetuximab to carboplatin plus a taxane (paclitaxel or docetaxel) in 
767 patients (see Table 3) [22]. In contrast to FLEX, EGFRI positivity 
was not required for study entry. In BMS 099, patients assigned to 
cetuximab had a survival benefit that was similar to that observed 
in the FLEX study both in absolute (1.3 months of difference in 
median OS) and in relative terms (HR 0.89, CI 0.75–1.05), but the 
difference was not statistically significant (stratified log–rank 
P = 0.17). Cetuximab was associated with an increase in objective 
response rate, without a difference in the primary study endpoint 
(median PFS 4.4 vs. 4.24 months; HR 0.902, CI 0.761–1.069, 
P = 0.24).

The results of the two phase III trials testing the addition of 
cetuximab to first-line treatment have been pooled, together with 
two randomized phase II studies [23,24], in a meta-analysis [25]. 
Overall, the four trials enrolled 2018 patients, with all histologic 
subtypes of NSCLC. The meta-analysis shows that the addition of 
cetuximab is associated with a statistically significant benefit both 
in terms of OS (HR 0.878, CI 0.795–0.969, P = 0.01) and PFS (HR 
0.899, CI 0.814–0.993, P = 0.036), without the evidence of hetero-
genrety among the studies.

There are several relevant issues about the interpretation of 
these results. First, the observed benefit from the addition of 
cetuximab to chemotherapy is small both in terms of HR (13% reduction 
in the risk of death) and in terms of absolute prolongation of sur-
vival (1.2 months of difference in median OS). This limited benefit 
could be the consequence of a clinically modest effect in all treated 
patients or could be driven by a relevant effect limited to a subgroup 
of patients. In the latter hypothesis, the identification of predic-
tive factors would be essential for the optimal use of the drug, but 
to date there are no conclusive molecular data to direct patient 
selection, although the predictive role of early skin toxicity is inter-
esting and deserves further investigation. Second, considering the 
negative results of BMS 099, whether the benefit observed with 
cisplatin and vinorelbine could be the same, smaller, or larger with 
other platinum-based doublets is unknown. Finally, cetuximab was 
administered, per protocol, as single agent until disease progression 
or unacceptable toxicity after completion of chemotherapy, but, 
as with bevacizumab, data supporting its efficacy as maintenance 
treatment are lacking.

On July 2009, the Committee for Medicinal Products for Human 
Use (CHMP) of EMEA adopted a negative opinion, recommend-
ing against marketing authorization for the addition of cetuximab 
treatment to chemotherapy for NSCLC (see Table 2). The CHMP 
was concerned that the benefits of adding cetuximab to standard 
platinum-based chemotherapy were modest in terms of survival 
times, and that the antibody did not produce a significant prolong-
ation of PFS or a significant improvement in health-related quality 
of life. The drug company requested re-examination of the nega-
tive opinion. However, the CHMP re-examined the initial opinion 
and confirmed the refusal of the marketing authorization on 19 
November 2009.

3.1.3. Pemetrexed plus cisplatin as first-line treatment

Pemetrexed, a potent inhibitor of thymidylate synthase and 
other folate-dependent enzymes, was approved in 2004 by both 
FDA and EMEA for the second-line treatment of advanced NSCLC. 
A large randomized phase III trial compared cisplatin plus peme-
trexed to cisplatin plus gemcitabine in the first-line setting [26]. 
The study was designed as a non-inferiority trial, with OS as the 
primary endpoint with the upper limit of 95% CI of the HR for cisplatin 
plus pemetrexed compared to cisplatin plus gemcitabine required 
to be lower than 1.17 to prove non-inferiority. This fixed margin 
would correspond to a 15% reduction in the risk of death in favor of 
standard treatment over pemetrexed, a difference that was judged 
by the authors to be the maximum acceptable difference. Overall, 
1725 patients with advanced NSCLC and good performance status

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Randomized phase III trials with cetuximab in addition to chemotherapy as first-line treatment of advanced non-small cell lung cancer.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control arm</td>
<td>Experimental arm</td>
</tr>
<tr>
<td>cisplatin 80 mg/m² + vinorelbine 25 mg/m², day 1 and 8 every 3 weeks for up to six cycles</td>
<td>cisplatin 80 mg/m² + vinorelbine 25 mg/m², day 1 and 8 every 3 weeks for up to six cycles</td>
</tr>
<tr>
<td>Carboplatin AUC 6 + docetaxel 75 mg/m² or paclitaxel 225 mg/m², day 1 every 3 weeks for up to six cycles</td>
<td>Carboplatin AUC 6 + docetaxel 75 mg/m² or paclitaxel 225 mg/m², day 1 every 3 weeks for up to six cycles</td>
</tr>
<tr>
<td>Number of patients assigned to control</td>
<td>568</td>
</tr>
<tr>
<td>Number of patients assigned to cetuximab</td>
<td>557</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>Overall survival</td>
</tr>
<tr>
<td>Median in cetuximab arm</td>
<td>11.3 months</td>
</tr>
<tr>
<td>Median in control arm</td>
<td>10.1 months</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.871 (0.762–0.996)</td>
</tr>
<tr>
<td>P (log–rank test)</td>
<td>0.044</td>
</tr>
<tr>
<td>Progression-free survival</td>
<td>Median in cetuximab arm</td>
</tr>
<tr>
<td>Median in control arm</td>
<td>4.8 months</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.943 (0.825–1.077)</td>
</tr>
<tr>
<td>P (log–rank test)</td>
<td>0.39</td>
</tr>
</tbody>
</table>

AUC, area under the concentration–time curve (mg per ml per minute); CI, confidence intervals; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer. 
* Per Independent Review Radiologists Committee (IRR).
(ECOG 0 or 1) were enrolled. The HR was 0.94 (CI 0.84–1.05), thus demonstrating the non-inferiority of cisplatin plus pemetrexed. Furthermore, the pemetrexed combination was characterized by a more favorable toxicity profile, with significantly lower rates of grade 3 or 4 neutropenia, anemia, thrombocytopenia, febrile neutropenia, hair loss, although a significantly higher incidence of grade 3 or 4 nausea.

Notably, subgroup analysis according to tumor histologic subtype showed significant interaction with treatment efficacy, with higher efficacy of cisplatin plus pemetrexed in non-squamous tumors and higher efficacy of cisplatin plus gemcitabine in squamous tumors. Overall survival was statistically superior for cisplatin plus pemetrexed vs. cisplatin plus gemcitabine in patients with adenocarcinoma (12.6 vs. 10.9 months, respectively) and large-cell carcinoma history (10.4 vs. 6.7 months, respectively). In contrast, in patients with squamous cell histology, there was a significant improvement in survival with cisplatin plus gemcitabine versus cisplatin plus pemetrexed (10.8 vs. 9.4 months, respectively). Treatment-by-histology interaction was statistically significant ($P<0.005$) for both OS and PFS [27]. Similar results in terms of treatment-by-histology interaction were obtained in a second-line trial comparing pemetrexed vs. docetaxel [27,28] and in a trial comparing pemetrexed to placebo as maintenance treatment after completion of first-line chemotherapy [29,30]. In contrast, no significant superiority for pemetrexed-based treatment in non-squamous tumors was apparent in the subgroup analysis of a smaller phase III trial comparing first-line carboplatin plus gemcitabine vs. carboplatin plus pemetrexed [31]. However, the consistency of the results across the other studies supports the predictive role of histology for pemetrexed efficacy and the survival benefit associated with pemetrexed in patients with non-squamous histology.

In 2008, pemetrexed was approved by both the EMEA and the FDA, in combination with cisplatin, as first-line treatment of patients with non-squamous NSCLC (see Table 2).

When discussing the results obtained with pemetrexed, the panelists emphasized that the trial was designed to demonstrate non-inferiority of cisplatin plus pemetrexed, and the primary interpretation of its results should be made accordingly. As a general rule, the results of subgroup analyses should not be over-interpreted and, even if supported by robust clinical and biological evidence, one should view them as hypothesis generating. However, the panelists agreed that the consistency of results across several trials testing pemetrexed-based treatment represents an element supporting the interaction between treatment and tumor histology. Available data suggest that pemetrexed should not be recommended for the treatment of squamous cell carcinoma. On the other hand, pemetrexed-based treatment may be considered a better option compared to cisplatin and gemcitabine for the first-line treatment of patients with non-squamous advanced NSCLC. Together with considerations related to treatment toxicity, treatment costs, and patient convenience, this treatment-by-histology interaction should be taken into account when choosing between platinum-based doublets in patients with advanced NSCLC.

3.1.4. Single-agent EGFR tyrosine-kinase inhibitors as first-line treatment

Gefitinib and erlotinib are small molecule, orally active, selective, and reversible EGFR-TKIs, that have been evaluated extensively in NSCLC. Despite promising preclinical results, showing that EGFR-TKIs can enhance the anti-tumor activity of chemotherapy, all four randomized trials that tested the concomitant addition of gefitinib or erlotinib to first-line chemotherapy of advanced NSCLC produced negative results [32–35]. Better results were obtained when gefitinib and erlotinib were administered as single agents in the second-line and third-line settings. Erlotinib significantly prolonged survival in NSCLC patients no more eligible for chemotherapy after the failure of one or two previous regimens [36]. In a similar trial [37], gefitinib did not produce a statistically significant benefit in the overall study population, but was significantly superior to placebo in the subgroups of never smokers and Asian patients. Furthermore, gefitinib was shown to be non-inferior to docetaxel as second-line treatment in a large international study [38] and in an individual patient data meta-analysis pooling together that trial with further three smaller studies [39]. Patients in these trials were not selected for therapy by clinical or molecular characteristics. Chance of activity of both drugs is substantially higher in patients carrying EGFR sensitizing mutations, but neither clinical characteristics that are associated with higher frequency of mutation (Asian origin, female gender, history of never or light smoking, adenocarcinoma) nor molecular features (EGFR mutation itself, EGFR protein expression, EGFR gene copy number or KRAS mutation) could identify subgroups of patients who definitely did not benefit from treatment [40,41].

The IPASS (Iressa Pan-Asia Study) randomized phase III trial compared gefitinib with carboplatin plus paclitaxel in 1217 Asian patients with advanced NSCLC who were not previously treated for advanced disease [42]. Patients were selected according to clinical factors (adenocarcinoma and either never smokers or former light smokers), but there was no selection based on molecular markers. The study was designed to demonstrate that gefitinib was non-inferior to chemotherapy with a primary endpoint of PFS. The investigators hypothesized that, in a clinically selected group of patients, first-line therapy with an EGFR-TKI would be at least as effective as chemotherapy, with benefits in tolerability and quality of life. The predefined non-inferiority margin was a HR 1.2 for gefitinib compared to chemotherapy. In fact, gefitinib demonstrated superiority compared to carboplatin and paclitaxel (HR for PFS 0.74, CI 0.65–0.85, $P<0.001$). Median PFS was similar (5.7 vs. 5.8 months; for gefinitib and chemotherapy, respectively), due to the crossing shape of the PFS curves, showing a better outcome with chemotherapy in the first 6 months, but subsequently favoring gefitinib. Final overall survival data are not yet available. Immature data, based on 37% of deaths, show a HR for death in the gefitinib group of 0.91 (CI 0.76–1.10). Gefitinib was superior to chemotherapy in terms of quality of life and showed a more favorable toxicity profile. Subgroup analysis based on molecular analyses was conducted on the subset of patients with tumor sample available for molecular analysis (30–36% of the total sample). In the subgroup of 437 patients analyzed for the presence of EGFR mutation, there was significant interaction between treatment and EGFR mutation status. Gefitinib was significantly better than chemotherapy in terms of PFS in patients with EGFR mutated tumors (HR for PFS 0.48, CI 0.36–0.64, $P<0.001$), whereas chemotherapy was significantly better in EGFR wild-type patients (HR for PFS 2.85, CI 2.05–3.98, $P<0.001$). This interaction was statistically significant ($P<0.001$). The analysis of OS according to mutational status, based on a smaller number of events, showed a HR for death with gefitinib of 0.78 (CI 0.50–1.20) in the subgroup with mutation and 1.38 (CI 0.92–2.09) in the subgroup without mutation (interaction test not available).

There are several relevant issues about the interpretation of these results. First, there is a question of applicability of these results to non-Asian patients, because the study cohort was entirely accrued in East Asia, where EGFR mutations in NSCLC are more common [43]. From this point of view, the study population is remarkably atypical: about 60% of the tested highly selected patients (IPASS) had EGFR mutations, while the proportion of EGFR mutated patients in the first-line setting in a Western population is lower and closer to ~10% [44]. Second, the primary endpoint was a surrogate endpoint (PFS) and definitive data for OS are still lacking. Third, interpretation of the results is conditioned by the highly sta-
tistically significant interaction between EGFR mutation status and treatment. As a general rule, although the interaction test is a more accurate tool than performing separate tests in subgroups, subgroup analysis should always be interpreted with caution, as stated above. When subgroup analysis is based on molecular analyses and information about the status of the marker is available only for a limited proportion of patients, this represents an additional bias that potentially makes the interpretation of results problematic and potentially unreliable. Unfortunately, in the case of advanced NSCLC, the amount of tumor tissue available for molecular analysis is often very small and inadequate.

Notably, a preplanned, interim analysis of a Japanese randomized trial comparing gefitinib vs. carboplatin plus paclitaxel as first-line treatment limited to patients whose tumors carry EGFR sensitizing mutations [45] confirmed the superiority of gefitinib in terms of PFS observed in the IPASS trial (median PFS 10.4 vs. 5.5 months; HR 0.357, CI 0.25–0.51, \( P < 0.001 \)) and led to suspension of accrual. Similarly, another Japanese randomized trial comparing gefitinib vs. cisplatin plus docetaxel in cases with EGFR sensitizing mutations [46] showed a significant superiority of gefitinib in terms of PFS (HR 0.49, CI 0.34–0.71, \( P < 0.001 \)).

Definitive results of these trials and of a similar trial with erlotinib sponsored by the Spanish Lung Cancer Group (EURTAC-SLCG, ClinicalTrials.gov identifier NCT00446225) will add relevant evidence to this topic. In July 2009, the EMEA granted marketing authorization for gefitinib for the treatment of locally advanced or metastatic NSCLC with sensitizing mutations of the EGFR gene, across all lines of therapy (see Table 2).

3.2. Maintenance treatment

Currently most guidelines recommend a limited number of cycles (four to six) for first-line chemotherapy for NSCLC [8–10,47]. Prolonged duration of first-line treatment recently has received great attention, due to the positive results of several studies that tested this strategy in patients without progression at the end of the planned cycles of chemotherapy (see Table 4). In principle, prolonged duration of treatment can be realized with chemotherapy (continuing one or all the drugs administered in as induction therapy or switching to a different agent) or with a targeted agent (continuing the same agent previously administered with chemotherapy as is common practice with bevacizumab and cetuximab, or starting a new targeted agent). Whether this strategy should be called maintenance treatment, or prolonged duration of treatment, or sequential treatment, or early administration of second-line treatment, remains a semantic matter [48]. However, recent positive results have been obtained with the administration of a single agent drug which are different from the drugs received during the initial cycles of first-line treatment [29,30,49–51].

3.2.1. Docetaxel

Efficacy of docetaxel as sequential treatment was tested in a randomized trial enrolling patients with advanced NSCLC without progression after four cycles of platinum-based chemotherapy (cisplatin or carboplatin plus gemcitabine or docetaxel or paclitaxel) [29,30]. Patients were randomized, in a 2:1 ratio, to docetaxel (500 mg/m\(^2\)) or placebo in 21-day cycles, with the addition of \( B_12 \), folic acid, and dexamethasone in both arms. The choice of drug or regimen as second-line treatment was not pre-determined per protocol. The primary endpoint was PFS, but the overall alpha error was controlled for both PFS and OS to guarantee an overall alpha level lower than 0.05. In the overall study population, docetaxel was significantly better than placebo both in terms of PFS (median 4.0 vs. 2.0 months; HR 0.60, CI 0.49–0.73, \( P < 0.0001 \)) and OS (median 13.4 vs. 10.6 months; HR 0.79, CI 0.65–0.95, \( P = 0.012 \)). Treatment with docetaxel was well tolerated, without treatment-related deaths and with few severe adverse events. Notably, pre-specified analysis of efficacy by tumor histology showed a significant interaction between treatment and histology, consistent with the similar analyses performed in other pemetrexed-based trials: pemetrexed produced significant and clinically meaningful benefit compared to placebo in the non-squamous group, both in terms of PFS and OS, while there was no benefit of maintenance pemetrexed in patients with squamous tumors.

The present study provides important evidence about the efficacy of pemetrexed as maintenance treatment, but the panel members noted that several methodological limitations should be considered when interpreting those results. First, there was no mandatory crossover in the control arm at disease progression. Less than 20% of patients assigned to placebo actually received pemetrexed. In the study conducted with docetaxel, all patients assigned to the control arm who were still eligible for chemotherapy at disease progression received docetaxel as second-line treatment [49]. This strategy, with OS as primary study endpoint, represents the optimal study design to test the efficacy of introducing a new agent before progression. Whether the relevant improvement in OS observed with maintenance pemetrexed would have been the same, or reduced, if the study had imposed crossover after progression is currently unknown. Second, none of the patients enrolled in the trial received pemetrexed as first-line chemotherapy as pemetrexed did not have a first-line indication at the time the study was performed. This raises the question as to whether the survival benefit was due to the introduction of a non-cross-resistant chemotherapeutic agent or simply due to the prolonged administration of chemotherapy. Whether this survival benefit could be achieved in patients treated with first-line pemetrexed is still unclear. This issue will be clarified by the results of the ongoing trial comparing pemetrexed vs. placebo in patients who do not progress following four cycles of pemetrexed plus cisplatin (ClinicalTrials.gov Identifier NCT00789373). A trial of similar design evaluating maintenance gemcitabine after induction gemcitabine and carboplatin may also help to address the issue of continued third-generation single agent versus introduction of a new agent. Third, patients enrolled in this trial did not receive bevacizumab as part of their first-line therapy, and it is tempting to speculate whether the benefit of maintenance treatment...
Recent phase III trials with maintenance/sequential treatment in patients not progressed after first-line treatment of advanced non-small cell lung cancer.

| Table 4 | Recent issues in first-line treatment of advanced non-small-cell lung cancer.

<table>
<thead>
<tr>
<th>Source</th>
<th>Eligibility criteria</th>
<th>Main results</th>
<th>Progression-free survival</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fidias et al. [48]</td>
<td>Number of patients assigned to control arm: 156, Number of patients assigned to experimental arm: 153, Primary endpoint: Overall survival, Eligibility criteria: Age: No upper limit, Performance status: ECOG 0–2, Histology: NSCLC, all subtypes</td>
<td>Median in experimental arm: 12.3 months, Median in control arm: 9.7 months, Hazard ratio (95% CI): 0.79 (0.65–0.95), P (log–rank test): 0.085</td>
<td>Median in experimental arm: 12.3 months, Median in control arm: 9.7 months, Hazard ratio (95% CI): 0.79 (0.65–0.95), P (log–rank test): 0.085</td>
<td>n.a.</td>
</tr>
<tr>
<td>JMEN [29,30]</td>
<td>Number of patients assigned to control arm: 441, Number of patients assigned to experimental arm: 438, Primary endpoint: Progression-free survival, Eligibility criteria: Age: No upper limit, Performance status: ECOG 0–1, Histology: NSCLC, all subtypes</td>
<td>Median in experimental arm: 13.4 months, Median in control arm: 10.6 months, Hazard ratio (95% CI): 0.79 (0.65–0.95), P (log–rank test): 0.012</td>
<td>Median in experimental arm: 13.4 months, Median in control arm: 10.6 months, Hazard ratio (95% CI): 0.79 (0.65–0.95), P (log–rank test): 0.012</td>
<td>0.71 (0.62–0.82), 0.0088</td>
</tr>
<tr>
<td>SATURN [50,53]</td>
<td>Number of patients assigned to control arm: 451, Number of patients assigned to experimental arm: 438, Primary endpoint: Progression-free survival, Eligibility criteria: Age: No upper limit, Performance status: ECOG 0–1, Histology: NSCLC, all subtypes</td>
<td>Median in experimental arm: 12.0 months, Median in control arm: 11.0 months, Hazard ratio (95% CI): 0.81 (0.70–0.95), P (log–rank test): 0.0088</td>
<td>Median in experimental arm: 12.0 months, Median in control arm: 11.0 months, Hazard ratio (95% CI): 0.81 (0.70–0.95), P (log–rank test): 0.0088</td>
<td>n.a.</td>
</tr>
<tr>
<td>ATLAS [51]</td>
<td>Number of patients assigned to control arm: 373 (as of 18 July 2008), Number of patients assigned to experimental arm: 370 (as of 18 July 2008), Primary endpoint: Progression-free survival, Eligibility criteria: Age: No upper limit, Performance status: ECOG 0–1, Histology: NSCLC, non-squamous</td>
<td>Median in experimental arm: 13.4 months, Median in control arm: 12.0 months, Hazard ratio (95% CI): 0.81 (0.70–0.95), P (log–rank test): 0.0088</td>
<td>Median in experimental arm: 13.4 months, Median in control arm: 12.0 months, Hazard ratio (95% CI): 0.81 (0.70–0.95), P (log–rank test): 0.0088</td>
<td>0.72 (0.59–0.88), 0.012</td>
</tr>
</tbody>
</table>

Cl: confidence intervals; ECOG, Eastern Cooperative Oncology Group; n.a.: data not available; NSCLC, non-small cell lung cancer.

Pemetrexed would apply also to patients receiving first-line induction and maintenance bevacizumab. Hopefully, currently ongoing trials (ClinicalTrials.gov ID NCT00961415) will clarify this issue.

Notwithstanding these limitations, these results were considered by the panelists as interesting evidence, supporting a potential role for pemetrexed in maintenance treatment of patients with advanced NSCLC of non-squamous histology.

In July 2009, both the FDA and the EMEA approved pemetrexed as maintenance therapy for metastatic NSCLC, specifically in patients with non-squamous histology whose disease has not progressed after platinum-based first-line chemotherapy (see Table 2).

### 3.2.3. Erlotinib

The SATURN randomized phase III study compared erlotinib with placebo as maintenance treatment for patients with non-progressive NSCLC after four cycles of first-line platinum-based chemotherapy [50]. Study population was not selected for any clinical or molecular factor although EGFR status was a stratification parameter. The primary endpoint of the study was PFS in the whole population, and the co-primary endpoint was PFS in EGFR-positive patients (HR 0.69, CI 0.58–0.82, P < 0.0001). The benefit associated with erlotinib in the subgroup of EGFR-positive patients (HR 0.69, CI 0.58–0.82, P < 0.0001) was similar to the result obtained in the whole population. Overall survival was a secondary endpoint of the study. Patients receiving erlotinib had a significantly longer survival than those receiving placebo (12 vs. 11 months; HR 0.81, P = 0.009). Tumor biomarker analyses were performed in a subset of patients with evaluable samples (49% for EGFR mutation, 55% for EGFR gene copy number and KRAS mutation, 83% for EGFR protein expression). There was no significant interaction between EGFR expression, EGFR gene copy number, and KRAS mutation and treatment efficacy in terms of PFS. Although the benefit associated with erlotinib treatment was statistically significant in EGFR wild-type as well as EGFR mutated tumors, a significant interaction between treatment and EGFR mutation status was demonstrated. The HR for PFS was 0.10 and 0.78 in EGFR mutated and EGFR wild-type patients, respectively (interaction P < 0.001). No significant difference in overall survival for the erlotinib arm was shown in the subgroup of EGFR patients whose tumors had mutations, but it should be noted that 67% of these patients assigned to the placebo arm received a second-line EGFR-TKI [52].

The role of erlotinib as maintenance treatment for patients without progression after first-line chemotherapy has been tested in another randomized phase III trial, the ATLAS study [51]. This study was designed to evaluate the addition of erlotinib to bevacizumab as maintenance treatment in patients receiving first-line bevacizumab and platinum-based chemotherapy. Eligibility was obviously limited to patients eligible for treatment with bevacizumab, excluding patients with squamous, central tumors, or other contraindications, but there was no selection for other clinical or molecular putative predictive factors. The primary endpoint was PFS. The Data Safety Monitoring Committee recommended stopping the trial after the second planned interim analysis because the study met its primary endpoint (median PFS 4.76 months for bevacizumab + erlotinib vs. 3.75 months for bevacizumab + placebo; HR
0.722, CI 0.59–0.88, P = 0.0012). Survival results and subset analyses based on molecular markers have not been reported to date.

Both studies conducted with erlotinib as maintenance treatment should be interpreted with caution. First, the primary endpoint was PFS. As in the pemetrexed trial, there was no mandatory crossover in the control arm at disease progression. Only a minority of patients assigned to placebo actually received an EGFR-TKI, although this is currently a standard second-line treatment option. Whether the improvement in OS observed with maintenance erlotinib would have been the same, or reduced, if the study had imposed crossover after progression is currently unknown. Second, the absolute benefit in overall survival was modest in the SATURN trial and still unknown in the ATLAS trial. Notably, the absolute benefit was much higher in the subgroup of EGFR mutated patients, with all the caveats of subgroup analyses based on biomarkers performed in a subset of study population. Notwithstanding these limitations, these results were considered by the panelists as interesting evidence supporting a potential role for erlotinib in maintenance treatment of patients with advanced NSCLC.

In March 2009, an application was submitted to both the EMEA and the FDA for the use of erlotinib as maintenance treatment of patients not progressing after first-line platinum-based chemotherapy of advanced NSCLC (see Table 2).

4. Consensus for clinical practice

4.1. Need for adequate tumor tissue and importance of accurate subtype diagnosis.

Panel members agreed that every effort should be made to obtain adequate tumor tissue in all patients who are candidates to receive treatment for advanced NSCLC. Until recently, treatment of NSCLC patients was substantially based on tumor stage and performance status, but, in the light of recent results, information about tumor subtype (in all patients) and some molecular characteristics (EGFR mutational status in selected patients) is considered relevant for the most appropriate management of these patients. In particular, the development of therapies that are more effective or less toxic when targeted to one particular subtype of NSCLC has conditioned the marketing authorization of several drugs (pemetrexed, bevacizumab) and this mandates obtaining an accurate histologic and molecular diagnosis. However, panelists noted that, while classifying a NSCLC into the appropriate histologic subtype can be relatively easy in patients whose tumors have been surgically resected, a pathological diagnosis based on cytology alone in advanced patients may be much more difficult. Routinely performed diagnostic procedures are increasingly less invasive, with minimal amount of neoplastic tissue or cells required to make a pathological diagnosis [54]. The histologic material for the diagnosis is often limited to small biopsy samples (of primary or metastatic tumors), causing the tumor-type classification to possibly be incorrect. Diagnostic reproducibility of tumor subtyping among different pathologists can be inadequate, and classification criteria need to be improved [55].

4.2. EGFR mutation analysis

Considering the low rate of EGFR mutation in Western patients [44], panelists do not recommend mutation analysis in all selected patients. However, given the possible use of EGFR-TKI as first-line treatment in cases with EGFR mutation, mutation analysis should be considered, when allowed by tumor tissue availability, in subgroups of patients bearing at least one of the clinical or pathological characteristics that are associated with higher prevalence of mutation (Asian, adenocarcinoma, never smokers, women) [44] (see Fig. 1).

If EGFR mutation analysis shows the presence of a sensitizing gene mutation, first-line single-agent EGFR-TKI therapy may be considered. This is based on the subgroup analysis of the IPASS study showing statistically significant interaction between treatment efficacy and the presence of mutation, and clinically relevant superiority of PFS for gefinitib compared to chemotherapy as first-line treatment in patients with EGFR mutation [42]. Patients with EGFR mutations, who are without progression after first-line chemotherapy, also obtain a relevant benefit from maintenance treatment with erlotinib [50]. In fact, although the PFS benefit of erlotinib as maintenance is statistically significant also in the wild-type group, the benefit is significantly greater in patients with EGFR mutation. Considering this significant interaction, even if EGFR mutational status is not available at the moment of starting first-line treatment, it could be potentially useful to obtain that information during the administration of first-line chemotherapy, in order to consider the opportunity of maintenance treatment with erlotinib.

At this time, clinical selection of patients for first-line therapy with an EGFR-TKI cannot be recommended.

4.3. Histologic subtyping

Panel members agreed unanimously that tumor histology/cytology subtyping is needed in order to select the optimal treatment of patients with advanced NSCLC.

Data currently available, that have been described in previous paragraphs, justify a division between (i) squamous and (ii) non-squamous tumors (see Figure 1).

4.4. Options for patients with squamous tumors

Patients with squamous NSCLC are not eligible for treatment with cisplatin plus pemetrexed (due to lower efficacy) nor for treatment with bevacizumab combined with chemotherapy (due to safety issues).

- In fit, adult patients with squamous tumors, the choice of first-line treatment is among the available platinum-based doublets (cisplatin or carboplatin with a third-generation drug), with the exception of cisplatin plus pemetrexed.
- Addition of cetuximab to platinum-based chemotherapy in EGFR-positive tumors is associated with some benefit. However, cetuximab currently is not approved for use in NSCLC in Europe or North America.

For patients not progressing at the end of first-line therapy, the opportunity of maintenance treatment with drugs approved for this use in clinical practice should be discussed with each patient on an individual basis. Of course, squamous tumors are not eligible for maintenance with pemetrexed or bevacizumab and, as of November 2009, cetuximab is not approved for use in clinical practice and erlotinib is still under evaluation at regulatory agencies.

4.4.1. Options for patients with non-squamous tumors

Patients with non-squamous histology currently are eligible for a broader number of treatments. Unfortunately, direct efficacy comparisons of the recent options (cisplatin plus pemetrexed, platinum-based chemotherapy plus bevacizumab, platinum-based chemotherapy plus cetuximab) are not available currently. Consequently, there are several possible treatment options that cannot be ranked in order of efficacy:
Among the different platinum-based doublets, cisplatin plus pemetrexed appears to be associated with higher efficacy and lower toxicity compared to cisplatin plus gemcitabine. On the other hand, there is no direct comparison of cisplatin plus pemetrexed versus other platinum-based doublets.

In patients without contraindications to bevacizumab, its addition to platinum-based chemotherapy is an option. When added to carboplatin plus paclitaxel, bevacizumab produced a significant prolongation of survival. When added to cisplatin plus gemcitabine, bevacizumab produced a statistically significant prolongation only of PFS.

Addition of cetuximab to platinum-based chemotherapy in EGFR-IHC-positive tumors is associated with some benefit. The drug is currently not approved for use in clinical practice.

For patients not progressing at the end of first-line, the opportunity of maintenance treatment with drugs approved for this use in clinical practice should be discussed with patients.

5. Issues for future clinical research in the first-line treatment of advanced NSCLC

With the aim of suggesting the priorities for clinical research in the treatment of advanced NSCLC, panel members identified some general and some specific issues (see Tables 5 and 6).

5.1. General issues

Unfortunately, most of the results obtained with new drugs, although determining new authorizations for use in clinical practice, represent only limited progress in the treatment of advanced NSCLC. This progress could be considered negligible in absolute terms, especially in some cases [56], especially considering the high cost of these new drugs. Participation in a prospective, well-designed clinical trial should be offered to every eligible patient.

The panel recommends the use of overall survival as the primary endpoint, whenever appropriate. This will help to document the real benefit for patients associated with new treatments. Furthermore, particular caution should be adopted when statistically significant results with lower than expected absolute advantages, of small clinical relevance, are observed. To reduce this risk, future clinical trials should be designed, and the sample size calculated to provide adequate statistical power to demonstrate clinically relevant differences between treatments. In other words, very large sample sizes that may result in statistically significant but clinically irrelevant improvements in absolute terms should be avoided.

Translational research is essential to identify predictive factors and should be performed, whenever feasible, in order to obtain treatment optimization. The need to identify predictive factors, however, should not determine an abuse of subgroup analyses that should be considered as non-definitive, hypotheses-generating evidence.

Health utilization data should be collected prospectively in all studies of new agents to allow for sound cost-effectiveness analyses (CEAs). Whenever possible, CEAs should be performed by independent investigators not supported by the pharmaceutical industry, using this prospective data collected throughout the entire lifespan of all patients (not just while on study therapy) from randomized trials with a standard treatment control arm. CEAs that are based on models should be considered less robust.

Academic and non-profit research should receive more funding in order to increase the volume of independent research.

5.2. Specific issues

Considering the limited efficacy of currently available options, prospective clinical trials of newly targeted agents represent a high research priority. Nevertheless, a number of relevant research priorities can be identified to optimize the use of available options:

• To date, there is limited comparative evidence among the different treatments available for patients eligible for multiple options (e.g., cisplatin plus pemetrexed vs. platinum-based chemotherapy plus bevacizumab in non-squamous tumors).

• Maintenance treatment has recently received great attention, after the positive results obtained with pemetrexed and with erlotinib. Experts agreed that stronger definitive evidence supporting the role of maintenance treatment could come from a
“strategy” design comparing the maintenance strategy with the standard administration of the same drug as second-line treatment, similar to the design of the trial performed with docetaxel [49]. The primary endpoint of such a trial should consequently be overall survival.

• To date, there is no comparative evidence among the different options available for maintenance treatment. Prospective comparison would be of great interest.

• Both bevacizumab and cetuximab, in the registration trials, were administered until disease progression, although the role of both drugs as maintenance treatment has not yet been investigated. In particular, the role of cetuximab or bevacizumab as maintenance could be clarified by a trial comparing their administration for a limited number of cycles, concomitant with chemotherapy, with their administration until disease progression. However, panel members considered this issue of medium priority.

• For all treatments, identification of predictive markers for treatment efficacy would be of essential relevance, in terms of optimization of patient benefit and costs. Prospective evaluation of predictive biomarkers, including non-tumor effects (e.g., skin rash with anti-EGFR drugs, hypertension with angiogenesis inhibitors) is of great interest, especially in the case of early-onset toxicity.

Conflict of interest statement

• C. Gridelli received honoraria for participation in advisory boards and symposia (Eli Lilly, Roche, Merck-Serono).

• A. Ardizzoni received honoraria as invited speaker (Eli Lilly, Roche).

• J.Y. Douillard received honoraria for participation in advisory boards and symposia (AstraZeneca, Pierre Fabre Oncologie, Roche, Merck-Serono, Sanofi-Aventis, Bristol-Myers Squibb, Pfizer, Boehringer Ingelheim, Novartis, Amgen).

• C. Manegold received honoraria for participation in advisory boards and symposia (AstraZeneca, Roche, Merck-Serono, Bristol-Myers Squibb, Boehringer Ingelheim, Novartis, Eli Lilly, Amgen).

• F. Perrone received honoraria for participation in advisory boards and symposia (Roche, Merck-Serono) and funding for clinical trials (Roche, Merck-Serono).

• R. Pirker received honoraria for participation in advisory boards and symposia (Roche, Merck-Serono, Eli Lilly).

• F.A. Shepherd received honoraria for participation in advisory boards and symposia (AstraZeneca, Pierre Fabre Oncologie, Roche, Merck-Serono, Sanofi-Aventis, Bristol-Myers Squibb, Pfizer, Boehringer Ingelheim, Novartis, Eli Lilly).

• M. Di Maio acted as consultant (Roche) and received honoraria for participation in advisory board (Eli Lilly).

• F. de Marinis received honoraria for participation in advisory boards and symposia (Roche, Merck-Serono, Novartis, Eli Lilly).

References


