Systemic therapy of advanced non-small cell lung cancer: Major-developments of the last 5-years

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KEYWORDS
Non-small cell lung cancer
Advanced disease
New systemic therapies

Abstract  The standard palliative treatment for advanced stage NSCLC remains a platinum doublet but by tailoring chemotherapy according to tumour histology the results can be improved through using pemetrexed-containing schemas in non-squamous-cell disease. In addition, maintenance chemotherapy appears to be effective in patients achieving clinical benefit by induction therapy. Targeted therapy based on the presence of activating epidermal growth factor receptor (EGFR) activating mutations or EML4–ALK gene rearrangement is becoming standard practice with high median survival rates, up to 30 months. There are still numerous other molecular targeted drugs in development. This review presents the most recent relevant progress in systemic anti-cancer therapy of advanced NSCLC in the past 5 years and delineates today’s new treatment options.

1. Introduction

Lung cancer is the second most common cancer in men and women and a leading cause of cancer-related deaths worldwide, with non-small cell lung cancer (NSCLC) representing approximately 85% of all cases. More than half of the patients are still diagnosed with advanced metastatic, disease and have a poor prognosis. Platinum-based palliative chemotherapy is considered a standard therapy for advanced disease, resulting in a median survival of 8–10 months with only 5% patients alive at 2 years. A recent randomised trial highlighted the importance of early palliative care given these poor outcomes. Patients assigned to early palliative care had a better quality of life (QoL) and lived longer compared to patients on standard care (which in most of the patients includes chemotherapy) alone.

Even though, some patients benefit from chemotherapy, the result of the ‘one size fits all’ approach to treatment in NCSLC is finally changing. During the last few years we have learnt that by tailoring chemotherapy according to tumour histology and/or the response to the first four cycles of chemotherapy, the results obtained by standard chemotherapy can be improved upon. Recent improved understanding of the molecular
biology of NSCLC has been followed by new, targeted therapies, and represents a major step forward in the treatment of this disease. This review presents the most recent relevant progress in systemic anti-cancer therapy of advanced NSCLC and delineates today’s new treatment options.

2. Chemotherapy

2.1. Platinum-based chemotherapy

The meta-analysis published in 1995 established the benefit of chemotherapy compared with supportive care alone (without chemotherapy) for advanced NSCLC. The updated meta-analysis, published in 2008 assessing newer platinum-based regimens incorporating third-generation cytotoxic drugs (gemcitabine, vinorelbine and paclitaxel), showed a further chemotherapy benefit (23% reduction of risk of death, 1-year survival gain of 9% and 1.5 months absolute increase in median survival). The results demonstrated a similar and robust benefit of chemotherapy across all patient subgroups, irrespective of tumour histology, patient age and performance status as well as progress with new drugs. Therefore, platinum-based regimens remain a gold standard of care for the treatment of advanced NSCLC patients. Yet another meta-analysis, published in 2007, compared the efficacy of two platinum agents, carboplatin and cisplatin, in advanced NSCLC. In the whole population, cisplatin treatment resulted in a significant increase in response rate (RR) (p < 0.001), without any significant benefit in overall survival (OS) (p = 0.100); while, in the subgroup of patients with non-squamous-cell tumours and those treated with the third-generation chemotherapy, carboplatin-based chemotherapy was associated with statistically significant increase in mortality. A major bias is related to the different doses of cisplatin and carboplatin used in the trials included in this meta-analysis. A recently reported prospectively randomised phase III study by British Thoracic Oncology Group Trial (BTOG) showed non-inferiority of carboplatin (AUC6) versus cisplatin (80 mg/m²) in combination with gemcitabine in terms of median OS (10 versus 9.5 months, p = NS). In addition, non-inferiority of lower cisplatin dose of 50 mg/m² compared to higher dose of 80 mg/m² has not been confirmed.

2.2. Individualised chemotherapy

Due to significant variations in response and survival of NSCLC patients receiving chemotherapy, there is a great need for new predictive markers for response. During the last 5 years encouraging results on the possible predictive value of two markers have emerged. The degree of expression of the thymidylate synthase (TS) enzyme appears to be a surrogate for observed differences in the efficacy of pemetrexed in different histologic subtypes of NSCLC, and excision repair cross complementing-1 protein (ERCC1) expression appears to be linked to the sensitivity to platinum-containing regimens.

The randomised trial of pemetrexed/cisplatin compared to gemcitabine/cisplatin in a preplanned analysis of outcomes by histology revealed statistically superior OS for pemetrexed/cisplatin compared with gemcitabine/cisplatin in non-squamous-cell histology (HR 0.81, 95% confidence interval (CI) = 0.70–0.94; p = 0.005), while OS was superior for gemcitabine-cisplatin in squamous cell histology. Of note, also in a retrospective analysis of the study evaluating the efficacy of pemetrexed alone versus docetaxel in a second line setting a significant interaction of the treatment outcome and histology was also demonstrated. Based on these results, pemetrexed containing regimens are the preferred treatment option for patients with non-squamous-cell histology and is thought to be due to lower levels of TS expression in the non-squamous group.

In NSCLC the relationship between ERCC1 expression and either better treatment response and/or longer survival after platinum-based chemotherapy has already been observed in numerous retrospective trials. Furthermore, the results of three meta-analyses published in the last 2 years support this hypothesis. To establish definitive value of ERCC1 as a predictive marker for response to platinum based chemotherapy the results of ongoing prospective clinical trials in both the advanced (ClinicalTrials.gov NCT00801736 and NCT00499109) and adjuvant setting (ClinicalTrials.gov NCT00775385) are eagerly awaited. In addition to ERCC1, other biomarkers (such as RRM1, BRCA1, RAP80 and beta globulin) with potentially predictive value for different chemotherapeutic schedules are being studied.

2.3. Chemotherapy in elderly

Lung cancer is a disease of older people, however they tend to be underrepresented in clinical trials of doublet chemotherapy. Until recently, elderly patients (>70 years) were mainly offered a third-generation single agent therapy, as this seemed the most appropriate conclusion from the trials in this age group. In two meta-analyses of these studies in the >70 years patients the doublet therapy was associated with a favourable RR but higher toxicity compared to monochemotherapy in both of the meta-analyses, however a statistically superior OS was observed in only one of these. Recently, a large prospective trial demonstrating a 4.1 month OS benefit with a carboplatin/paclitaxel combination over single agent therapy (vinorelbine or gemcitabine) in patients with a median age of 77 years has been reported. This improvement again came at
the cost of increased toxicity (6.6% versus 1.8% toxic deaths). Doublet chemotherapy seems to be a preferred option for fit elderly patients with a good performance status and without major comorbidities. Elderly patients appear to get the same benefits from newer treatments including targeted treatments. However, we have still not found a score that will help us select these patients in a more comprehensive fashion.

2.4. Anti-angiogenic treatment with chemotherapy

Due to clear association between squamous-cell histology and increased risk of major bleeding observed in phase 2 trials, only patients with non-squamous-cell histology were included in phase 3 trials of a humanised monoclonal antibody to vascular endothelial growth factor (VEGF). In the ECOG 4599 trial, bevacizumab added to paclitaxel/carboplatin improved median progression-free survival (PFS) and OS by 2 months (6.2 versus 4.5 months; HR 0.66; p < 0.001 and 12.3 versus 10.3 months; HR 0.79; p = 0.003, respectively), while in the confirmatory AVAiL trial bevacizumab added to cisplatin/gemcitabine improved PFS but failed to confirm significant prolongation in OS. So far, trials evaluating other anti-angiogenic agents, i.e., sorafenib, vandetanib, and motesanib failed to demonstrate survival benefit over chemotherapy alone or placebo in unselected advanced NSCLC patients. To improve the efficacy of these agents relevant molecular markers need to be identified.

2.5. Maintenance chemotherapy

The standard approach in using chemotherapy in advanced NSCLC has been to use a maximum of 4–6 cycles of a platinum-based doublet to maximum response and then stop. This approach has been based on the results of the prospective randomised clinical trials and meta-analysis showing that more than four cycles of platinum-based doublets do not improve survival but are associated with significant toxicity in patients with advanced NSCLC.

In the landmark trial comparing immediate switch maintenance therapy with docetaxel after four cycles of induction platinum-based chemotherapy with delayed docetaxel given only at the time of documented progression significantly longer PFS (5.7 versus 2.7 months, p = 0.0001) with a trend to better OS was demonstrated in the arm with immediate maintenance compared to delayed docetaxel. However, only 63% of patients in the delayed arm actually received the planned docetaxel therapy, mainly due to symptom deterioration and declining performance status at the time of progression, thus leading to the conclusion that advanced NSCLC patients are more likely to get second line therapy and experience its potential benefits if it is offered immediately after front-line treatment.

While in three large phase 3 trials no significant benefit, in terms of PFS or OS, was demonstrated by continuation maintenance with paclitaxel or gemcitabine, or switch to vinorelbine, in two other phase 3 trials significant benefit in terms of PFS, but not OS, was observed by continuation of gemcitabine therapy (Table 1). In the most recent and only positive switch maintenance study, the JMEN trial patients without progression after four cycles of platinum-based chemotherapy without pemetrexed were randomised to pemetrexed or placebo; and maintenance treatment with pemetrexed resulted in significant improvement of both PFS and OS in patients with non-squamous-cell compared to squamous-cell histology (PFS HR of 0.47 (p = 0.00001, interaction p value 0.036) and OS HR of 0.70 (p = 0.002, interaction p value 0.033). Maintenance pemetrexed also resulted in delayed time to worsening of symptoms without deterioration of QoL. In the AVA-PERL trial continuation chemotherapy with pemetrexed in addition to bevacizumab resulted in significant improvement of PFS and a trend to better OS in patients with non-squamous-cell NSCLC.

In the recently published PARAMOUNT trial, patients with non-squamous-cell histology not progressing on cisplatin/pemetrexed induction therapy were randomised to continued maintenance pemetrexed or placebo; and again pemetrexed resulted in a significant improvement of both, PFS (4.1 versus 2.8 months; HR 0.62, 95% CI: 0.49–0.79; p < 0.0001) and OS (13.9 versus 11.0 months; HR 0.78, 95% CI: 0.64–0.96; p = 0.0195). Of note, no patients in the placebo arm were offered pemetrexed as second-line therapy even if they had responded to it initially in this particular trial. There are several other issues regarding design and execution of these trials that might question the relevance of trials conclusions for optimal use of maintenance therapy in routine clinical practice. Nowadays, maintenance chemotherapy with single cytotoxic agent might be considered in fit advanced NSCLC patients achieving clinical benefit from induction platinum doublets.

3. Targeted therapies

3.1. Epidermal growth factor receptor (EGFR)-directed therapy

The major advances in the treatment of NSCLC during the last 5 years are due to the discovery of activating EGFR mutations as well as the introduction of reversible tyrosine kinase inhibitors (TKIs) of EGFR in all lines of treatment of EGFR mutated disease. First-generation EGFR TKIs, gefitinib and erlotinib, were initially studied in unselected populations of NSCLC patients in which they have demonstrated modest
activity in second- and third-line treatment. The predictive value of EGFR activating mutations (mostly exon-19 deletions and exon-21 L858R point mutations) for better RR and PFS to both TKIs, erlotinib and gefitinib, was first confirmed by retrospective analyses performed in the frame of prospective randomised studies comparing erlotinib/gefitinib versus chemotherapy/plac ebo in unselected population of pre-treated patients. In the last 5 years, the significant benefit of EGFR-directed first-generation TKIs over standard first-line chemotherapy in EGFR mutated patients has been confirmed by five large prospective randomised clinical trials conducted in Asian patients as well as in the recently published EURTAC trial conducted in a non-Asian population. Treatment with EGFR-directed TKIs was associated with a more favourable toxicity profile compared to chemotherapy and improved quality of life. Impressive median OS rates, ranging from 21.6 up to 30.5 months, have been observed. The comparative OS end-point was confounded by high crossover rates, with up to 94.6% of patients experiencing TKI therapy after failure of chemotherapy suggesting that these are very effective agents in the second and third-line settings. EGFR-directed TKIs represent an improved treatment option for EGFR mutation-positive patients. Despite encouraging RR and PFS achieved by the first-generation TKIs in patients with EGFR mutation-positive advanced NSCLC, resistance still occurs and various drugs targeted to the resistance pathways are being developed. Afatinib is one of the first irreversible ErbB2.

### Table 1

**Randomised studies of maintenance chemotherapy in advanced non-small cell lung cancer (NSCLC).**

<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>Induction therapy</th>
<th>Maintenance therapy and control arm</th>
<th>Number of patients</th>
<th>Median PFS (months)</th>
<th>Median OS (months)</th>
</tr>
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<tr>
<td><strong>Continuation maintenance chemotherapy</strong></td>
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<tr>
<td>North American Study (Belani et al., 2003)²⁶</td>
<td>Carboplatin/paclitaxel</td>
<td>Paclitaxel versus observation</td>
<td>401</td>
<td>38 weeks</td>
<td>75 weeks</td>
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<td>29 weeks</td>
<td>60 weeks</td>
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<td></td>
<td>p = NR</td>
<td>p = NR</td>
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<tr>
<td>CECOG (Brodowicz et al., 2006)²⁹</td>
<td>Cisplatin/gemcitabine</td>
<td>Gemcitabine versus BSC</td>
<td>206</td>
<td>6.6</td>
<td>13.0</td>
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<td>5.0</td>
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<td></td>
<td>p &lt; 0.001</td>
<td>p = 0.172</td>
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<tr>
<td>POI-01-003 (Belani et al., 2010)³⁷</td>
<td>Carboplatin/gemcitabine</td>
<td>Gemcitabine versus BSC</td>
<td>255</td>
<td>7.4</td>
<td>8.0</td>
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<td>7.7</td>
<td>9.3</td>
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<td>p = 0.575</td>
<td>p = 0.838</td>
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<tr>
<td>IFCT-GFPC (Perol et al., 2010)³⁰</td>
<td>Cisplatin/gemcitabine</td>
<td>Gemcitabine versus BSC</td>
<td>310</td>
<td>3.8</td>
<td>NR</td>
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<td>1.9</td>
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<td>p &lt; 0.0001</td>
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<tr>
<td>AVAPERL (Barlesi et al., 2011)³³</td>
<td>Cisplatin/ pemetrexed/bevacizumab</td>
<td>Bevacizumab/pemetrexed versus Bevacizumab/BSC</td>
<td>253</td>
<td>10.2</td>
<td>15.7</td>
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<td>6.6</td>
<td>p = 0.23</td>
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<td>p &lt; 0.001</td>
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<tr>
<td>PARAMOUNT (Paz-Ares et al., 2012)³⁴</td>
<td>Cisplatin/ pemetrexed</td>
<td>Pemetrexed versus BSC</td>
<td>539</td>
<td>4.1</td>
<td>13.9</td>
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<td>2.8</td>
<td>11.0</td>
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<td>p &lt; 0.0001</td>
<td>p = 0.0195</td>
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<td></td>
<td><strong>Switch maintenance chemotherapy</strong></td>
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<tr>
<td>GCOT (Westeel et al., 2005)³⁶</td>
<td>Mitomycin/ifosfamide/cisplatin</td>
<td>Vinorelbine versus observation</td>
<td>181</td>
<td>5.0</td>
<td>12.3</td>
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<td>3.0</td>
<td>12.3</td>
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<td></td>
<td>p = 0.11</td>
<td>p = 0.065</td>
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<tr>
<td>Immediate compared with delayed docetaxel after front-line Cht (Fidias et al., 2009)²⁵</td>
<td>Carboplatin/gemcitabine</td>
<td>Immediate docetaxel versus delayed docetaxel</td>
<td>309</td>
<td>5.7</td>
<td>12.3</td>
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<td>2.7</td>
<td>9.7</td>
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<td></td>
<td>p = 0.001</td>
<td>p = 0.085</td>
</tr>
<tr>
<td>JMEM (Ciuleanu et al., 2009)³¹</td>
<td>Platinum based Cht</td>
<td>Pemetrexed versus placebo</td>
<td>663</td>
<td>4.0</td>
<td>13.4</td>
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<td>2.0</td>
<td>10.6</td>
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<td>p &lt; 0.0001</td>
<td>p = 0.012</td>
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**Abbreviations:** OS, overall survival; PFS, progression-free survival; RR, response rate; HR, hazard ratio; NR, not reported; BSC, best supportive care.

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Please cite this article in press as: Cufer T. et al., Systemic therapy of advanced non-small cell lung cancer: Major-developments of the last 5-years, *Eur J Cancer* (2012), http://dx.doi.org/10.1016/j.ejca.2012.11.021
family inhibitors from the second-generation TKIs. In the LUX-Lung 3 trial,46 first-line therapy with afatinib demonstrated a significant improvement in PFS compared to cisplatin/pemetrexed (11.1 versus 6.9 months; HR 0.58, 95% CI: 0.43–0.78; p = 0.0004) and significant delay in time to deterioration of cancer-related symptoms of cough (HR 0.60; p = 0.0072) and dyspnoea (HR 0.68; p = 0.0145). This drug also has activity in heavily pretreated patients,47 thus giving more options for these patients with EGFR mutations. The efficacy of yet another second-generation TKI dacomitinib, an irreversible pan ErbB receptor TKI, the third-generation TKIs, such as dasatinib, SRC-family protein TKI and multiple others targeted agents are also being evaluated.

3.2. EGFR-directed therapy with chemotherapy

TKIs have a different mechanism of action, are active as single agents in a substantial proportion of patients with NSCLC, and have a distinct toxicity profile not overlapping with that of classical cytotoxic agents. As such, these drugs should be ideal for incorporation into chemotherapy schedules. It was a great disappointment when four prospective randomised trials showed overlapping curves of PFS and OS with chemotherapy and concomitant gefitinib48,49 or erlotinib50,51 compared to chemotherapy alone. However, in preclinical models and early phase non-comparative trials separation of chemotherapy and TKIs did show a synergistic effect. Recently presented results of the prospective, randomised phase 3 FASTACT-2 trial52 showed significantly prolonged PFS and OS with intercalated erlotinib (days 15–28) with chemotherapy compared to chemotherapy alone in EGFR mutated patients. Despite a mandatory crossover to erlotinib in EGFR mutated patients (85% crossed-over) significant benefit of overall survival was still noted. Intercalating therapy with TKIs and chemotherapy represents a treatment strategy that needs to be further evaluated in comparison to standard first line TKI therapy in EGFR mutated patents.

An EGFR-directed antibody, cetuximab, has been studied in combination with chemotherapy in advanced NSCLC as well. In the FLEX trial53 cetuximab added to cisplatin/vinorelbine improved RR and OS (11.3 versus 10.1 months, p = 0.044), but not PFS in EGFR protein expression positive patients; while54 the addition of cetuximab to carboplatin/docetaxel failed to improve PFS and OS in unselected patients. Notably, by retrospective biomarker analysis no predictive value of EGFR copy number, EGFR mutations or even KRAS mutations for response to cetuximab was confirmed in these trials.55,56 Based on unplanned retrospective analysis of the FLEX trial there is a hypothesis that a high EGFR protein expression score (H score > 200) might predict for better response to cetuximab.57 The efficacy of cetuximab in EGFR mutated patients has to be further defined and other biomarkers of response in EGFR wild patients need to be found.

3.3. ALK-directed therapy

Yet another important development in the targeted therapy of NSCLC has been achieved recently. Patients with alterations in the EML4–ALK fusion gene (alk–met translocation; approximately 4% of mostly adenocarcinomas) demonstrated an extraordinary response to the MET and ALK oral inhibitor crizotinib. In an extended phase 1 trial reported by Kwak et al.58 patients with advanced NSCLC with the alk–met translocation, who tend to be younger, never-smokers or light-smokers,
EGFR wild-type, and male, had a high 57% RR. With longer follow-up high 1-year and 2-year OS rates of 74% and 54%, respectively have been confirmed.\(^5^9\) At the last ESMO meeting in September 2012 results of the phase 3, PROFILE 1007 trial, evaluating efficacy of crizotinib versus chemotherapy with docetaxel or pemetrexed in the second-line setting were presented. In 342 ALK-positive patients crizotinib showed significant improvement in PFS (7.7 versus 3.0 months; HR 0.49, 95% CI: 0.37–0.64; \(p<0.0001\)) and RR (65% versus 20%; \(p<0.0001\)) compared to chemotherapy, with an acceptable toxicity profile.\(^6^0\) Due to high crossover (87% of pts.) no significant difference in OS was observed, however reported overall survival rates of patients included in PROFILE 1007 are remarkably high (preliminary median OS estimate 20.3 versus 22.8 months). These results established crizotinib as the standard of care for ALK-positive patients. It would now appear that ROS is also a target for crizotinib. Multiple other ALK and MET inhibitors are currently under development. Other targets are also being addressed in clinical trials. MEK inhibitors (a component of MAP kinase pathway), such as selumetinib, are currently being tested in KRAS mutated patients in ongoing phase 2 trials (ClinicalTrials.gov NCT01229150 and NCT01362296). Among several heat shock protein 90 (Hsp90) inhibitors, ganetespib (STA-9090) and AUY922 are being tested in multiple phase 2 (ClinicalTrials.gov NCT01562015, NCT01031225, NCT01124864, NCT01259089) and phase 2b/3 trials (ClinicalTrials.gov NCT01348126). Among other promising drugs, immune treatment with different types of vaccines is currently being evaluated in the field of NSCLC as well (Table 3).
3.4. Maintenance targeted therapy

In the earlier trials of platinum doublets with bevacizumab, cetuximab or EGFR TKIs these targeted agents were given in both the induction and in a continuous maintenance phase. During the last 5 years the results of five large prospective randomised trials evaluating a role of switch maintenance targeted therapy with EGFR directed TKIs, erlotinib or gefinitinib in responding or stable patients after four cycles of induction platinum based-doublets, have been published. Unfortunately, all these trials have been conducted in populations of advanced NSCLC patients with unknown or unselected for EGFR mutation status. In the SATURN trial, a significant prolongation of both, PFS and OS (HR = 0.71, p < 0.0001 and HR = 0.81, p = 0.0088, respectively) was demonstrated for maintenance erlotinib compared to placebo in the whole population. However, biomarker analysis showed a highly significant treatment by EGFR mutation interaction test (p < 0.001). Maintenance erlotinib has also been studied in the ATLAS trial comparing bevacizumab therapy with or without erlotinib after induction chemotherapy and in the French group trial comparing continuation maintenance gemcitabine and switch maintenance erlotinib with observation. In both these trials, maintenance erlotinib treatment resulted in small, but significant improvement in PFS, but not OS in an unselected population. Gefitinib has also been assessed as switch maintenance treatment in unselected population of NSCLC patients in two randomised trials (INFORM, EORTC 08021). In both trials patients treated with maintenance gefitinib experienced significantly longer PFS compared with placebo, but not OS. Of note, in the INFORM trial, patients with activating EGFR mutations derived significant benefit from maintenance gefitinib (HR = 0.17) while in patients with EGFR wild-type tumours the benefit of maintenance gefitinib was only marginal (HR = 0.86). There has been one negative phase 2 trial of maintenance therapy with the dual EGFR and VEGF TKI vandetanib in NSCLC.

The EORTC lung cancer group is conducting a prospective randomised phase 3 trial of maintenance pemetrexed versus placebo in patients not progressing after first-line platinum based chemotherapy (MAPPING trial). Sunitinib is being evaluated against placebo as maintenance treatment for advanced NSCLC in the CALGB randomised, phase 3 trial (ClinicalTrials.gov NCT00693992).

3.5. Treatment targeted to bone metastases

In recent years, bisphosphonates are an approved pharmacological intervention preventing and delaying skeletal related events (SRE) in NSCLC patients with bone metastases. Zoledronic acid is registered for the treatment of bone metastases in most tumour types including NSCLC but is underuse. Denosumab, a new bone targeted agent with less nephrotoxicity and comparable efficacy to zoledronic acid may be the most suitable agent to be combined with platinum-based therapy in NSCLC patients and needs further trials in NSCLC.

4. Conclusions

During the last 5 years major advances have been made in individualising systemic therapy for advanced NSCLC. The standard chemotherapy can already be tailored based on tumour histology, with pemetrexed being effective mainly in patients with non-squamous-cell histology. Overall survival benefits in maintenance chemotherapy are dominated by pemetrexed results in the SATURN trial, a significant prolongation of both, PFS and OS (HR = 0.71, p < 0.0001 and HR = 0.81, p = 0.0088, respectively) was demonstrated for maintenance erlotinib compared to placebo in the whole population. However, biomarker analysis showed a highly significant treatment by EGFR mutation interaction test (p < 0.001). Maintenance erlotinib has also been studied in the ATLAS trial comparing bevacizumab therapy with or without erlotinib after induction chemotherapy and in the French group trial comparing continuation maintenance gemcitabine and switch maintenance erlotinib with observation. In both these trials, maintenance erlotinib treatment resulted in small, but significant improvement in PFS, but not OS in an unselected population. Gefitinib has also been assessed as switch maintenance treatment in unselected population of NSCLC patients in two randomised trials (INFORM, EORTC 08021). In both trials patients treated with maintenance gefitinib experienced significantly longer PFS compared with placebo, but not OS. Of note, in the INFORM trial, patients with activating EGFR mutations derived significant benefit from maintenance gefitinib (HR = 0.17) while in patients with EGFR wild-type tumours the benefit of maintenance gefitinib was only marginal (HR = 0.86). There has been one negative phase 2 trial of maintenance therapy with the dual EGFR and VEGF TKI vandetanib in NSCLC.

In summary, important steps towards personalised treatment in lung cancer have been made within the last few years, and we need to take advantage of these opportunities to improve care and prolong survival in patients with NSCLC.

Conflict of interest statement

None declared.

References


