Most patients with non-small cell lung cancer (NSCLC) present with advanced, metastatic disease. Although treatment of these patients was recently improved with the discovery of EGFR and ALK targeting, molecular targeted drugs, most patients require chemotherapy. The outcome of patients with advanced NSCLC lacking EGFR or ALK mutations remains disappointing, with a median overall survival of 12–14 months. To improve survival and quality of life, the concept of maintenance therapy after first-line chemotherapy has gained interest, especially in the light of efficacious and better tolerable drugs and the results of recent clinical trials. However, the topic of maintenance therapy remains controversial and complex. Therefore, we give an overview on the current evidence and discuss our personal recommendations for clinical practice.

Keywords: Lung cancer, maintenance chemotherapy, tyrosine kinase inhibitors

Introduction

Despite global programs for tobacco prevention and smoking cessation, non-small cell lung cancer (NSCLC) remains the leading cause of cancer death in the developed world [1]. The majority of NSCLC patients present with advanced, metastatic disease at the time of diagnosis. Cytotoxic chemotherapy in these patients provides palliation and prolongs survival compared with best supportive care (BSC) [2]. Approximately 50% or less of these patients receive second-line therapy [3, 4], although second-line therapy can also prolong survival and improve quality of life [5–7]. Apart from the development of new drugs and personalized medicine, another strategy to improve patient outcome is to utilize maintenance therapy. This concept originates from haematology-oncology and, adopted to NSCLC, refers to immediate therapy after four to six cycles of standard first-line (or “induction”) therapy. “Continuation maintenance” stands for the continuation of at least one of the drugs used in first-line therapy, and “switch maintenance” for the use of a different drug. The term “maintenance” mandates that the tumour is in remission or stable after first-line therapy. If the tumour is progressing, change to a non-cross-resistant treatment is generally indicated, which is then denominated as second-line therapy.

The aim of prolonging the first-line therapy is to delay tumour progression, prolong survival and optimize quality of life with a minimum of side effects, especially cumulative toxicities. A reduction in cancer-related symptoms such as anorexia or fatigue should be balanced against the toxicities of continued chemotherapy. Consideration of the cost-benefit ratio is also important. One of the arguments in favour of maintenance therapy is that patients are generally in a better overall condition if therapy is started earlier. Another argument is that using new drugs early after first-line therapy has a potential advantage, because according to the Goldie and Coldman hypothesis, the proportion of chemotherapy-resistant cells in a tumour increases over time [8].

Continuation maintenance

Combination chemotherapy

Several trials showed no significant differences in survival or quality of life (QoL) between patients undergoing a short or long-duration of combination chemotherapy [4, 9–12]. These studies demonstrate that continuation of combination chemotherapy beyond a defined number of cycles did not provide additional benefit, but it was associated with higher clinically relevant toxicities. These data led to a change in the guidelines and established four (instead of six) cycles of platinum-based first-line therapy as the standard of care for patients with metastatic NSCLC [13].

Single-agent chemotherapy

A trial evaluating maintenance gemcitabine versus BSC after the initial treatment of four cycles of cisplatin and gemcitabine resulted in a prolonged time to disease progression (TTP) (6.6 vs. 5 months, p < 0.001), without a significant improve-
ment in overall survival (OS) [14]. Patients receiving maintenance therapy with gemcitabine showed significantly more haematologic toxicity and requirement of blood transfusions (20% vs. 6.3%, p = 0.018). Another trial presented at ASCO 2010 failed to show a survival benefit with maintenance gemcitabine after first-line therapy with carboplatin and gemcitabine [15]. In this study more than 50% of patients had an ECOG performance status (PS) of 2 or more. The IFCT-GFPC 0502 trial randomized patients after first-line therapy with cisplatin and gemcitabine to observation, a continuation maintenance arm with gemcitabine or a switch therapy with maintenance arm with erlotinib. In case of progression, all patients received pemetrexed. In a preliminary analysis, there was a significant benefit in PFS for both maintenance arms (gemcitabine HR 0.55, p < 0.0001; erlotinib HR 0.82, p = 0.002), but no OS benefit [16]. The results from the direct comparison of pemetrexed and erlotinib as well as results from biomarker analysis have not been reported yet. Interpreting these trials, the role of continuation maintenance therapy with single-agent gemcitabine does not appear very promising as none of the studies showed a survival benefit.

**Antibodies**

The two registration trials testing the anti-VEGF antibody bevazizumab in patients with advanced NSCLC both included bevazizumab maintenance until progression [17, 18]. The same was true for the FLEX and the BMS-99 trials testing the monoclonal anti-EGFR antibody cetuximab [19, 20]. All these trials did not randomize patients after first-line therapy to maintenance with the antibody versus control, so the benefit of continuation maintenance therapy with antibodies directed against VEGF or EGFR remains to be elucidated.

**Switch maintenance**

**Chemotherapy**

With the availability of the “third generation” cytotoxic agents, switch maintenance became a field of intensive clinical investigation. The following drugs were investigated in this indication: vinorelbine [21], docetaxel [22], and pemetrexed [23] (Tab. 1). The trial by Fidias et al. evaluated docetaxel starting immediately after first-line treatment with carboplatin and gemcitabine versus delayed docetaxel at the time of radiological or clinical disease progression. There was significant benefit in progression-free survival (PFS) with maintenance therapy. However, computed tomography was not performed at equal intervals in both arms. Patients in the delayed docetaxel arm underwent disease assessment every 3 months whereas patients in the immediate docetaxel arm were evaluated every 6 weeks. Furthermore, 37% of the patients in the delayed arm did not receive docetaxel at the time of progression. Interestingly, the median OS time for the safety population in both arms was identical (12.5 months) [22]. This may underline the importance of an active surveillance in patients not receiving maintenance treatment and starting a second-line therapy early enough. The JMEN trial by Belani et al. randomized patients with non-progressive disease after four cycles of platinum-based first-line therapy to pemetrexed or placebo. Patients receiving early pemetrexed had significantly prolonged PFS (HR 0.60, p < 0.00001) and OS (HR 0.79, p = 0.012). In a preplanned subgroup analysis, only patients with non-squamous histology showed prolonged OS (HR 0.70, p = 0.002 vs. HR 1.07 for squamous cell carcinoma) [23]. This finding was consistent with other trials evaluating pemetrexed, demonstrating that pemetrexed is not very active in squamous cell NSCLC [24, 25]. Moreover, in a subgroup analysis the benefit for pemetrexed maintenance was limited to patients with stable disease after first-line therapy, whereas patients with remission (CR or PR) had no significant prolongation of OS [26]. One limitation of the trial is that only 67% of patients in the placebo arm received second-line therapy, and only 18% received pemetrexed.

A recently published meta-analysis evaluating 2416 patients out of 13 trials of maintenance therapy demonstrated a substantial improvement in PFS with prolonged chemotherapy (HR 0.75, p < 0.00001). This benefit was more pronounced when third generation chemotherapy drugs were used, compared to older drugs (HR 0.73 vs. 0.92, p = 0.02). For overall survival, there was only a modest but significant benefit with maintenance chemotherapy (HR 0.92, p = 0.03). The OS benefit was mainly due to the pemetrexed trial [23]. Importantly, toxicities were consistently higher for patients receiving maintenance therapy. QOL, investigated in some of the included trials, was not improved with maintenance therapy in the meta-analysis [27].

**EGFR inhibitors**

Switching after first-line chemotherapy to EGFR tyrosine kinase inhibitors offers to patients a convenient oral treatment with a favourable toxicity profile. This strategy is also supported by preclinical data [28, 29]. One of the first trials of switch

### Tab. 1: Largest clinical phase III trials evaluating switch maintenance therapy with single-agent chemotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>1st-line therapy</th>
<th>Maintenance therapy</th>
<th>PFS [mo]</th>
<th>OS [mo]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brodowicz et al. [14]</td>
<td>352</td>
<td>Cis + Gem</td>
<td>Gem vs. Placebo</td>
<td>3.6 vs. 2.0*</td>
<td>10.2 vs. 8.1</td>
</tr>
<tr>
<td>Westeel et al. [21]</td>
<td>573</td>
<td>MMC + Ifosfamide + Cis</td>
<td>Vin vs. Placebo</td>
<td>5 vs. 3</td>
<td>12.3 vs. 12.3</td>
</tr>
<tr>
<td>Fidias et al. [22]</td>
<td>566</td>
<td>Cis + Gem</td>
<td>Docetaxel (maintenance vs. salvage)</td>
<td>5.7 vs. 2.7*</td>
<td>12.3 vs. 9.7</td>
</tr>
<tr>
<td>Ciuleanu et al. [23]</td>
<td>663</td>
<td>Platinum-doublet</td>
<td>Pem vs. Placebo</td>
<td>4 vs. 2*</td>
<td>13.4 vs. 10.6*</td>
</tr>
<tr>
<td>IFCT-GFPC 0502 et al. [16]</td>
<td>464</td>
<td>Cis + Gem</td>
<td>Gem vs. Erlotinib (E) vs. Placebo</td>
<td>HR 0.51 (Gem)</td>
<td>HR 0.63 (E)</td>
</tr>
</tbody>
</table>

* Cis cisplatin, Gem gemcitabine, MMC mitomycin-c, Vin vinorelbine, Pem pemetrexed, *p<0.05.
maintenance with molecular targeted agents used gefitinib. Patients without progression after three cycles of chemotherapy were randomized to gefitinib or three additional cycles of the same chemotherapy. Gefitinib prolonged PFS (HR 0.68, p < 0.001) but not OS, which may be caused by cross-over in 27% of the patients in the chemotherapy arm [30]. Another trial with gefitinib was presented at ASCO 2010 and confirmed these results [31]. The SATURN (Sequential Tarceva in Unresectable Lung Cancer) trial investigated maintenance with erlotinib in patients without progressive disease after 4 cycles of platinum-based first-line therapy. There was a significant survival benefit with erlotinib for PFS (HR 0.71, p < 0.0001) and OS (HR 0.81, p = 0.0088). For patients with a sensitizing EGFR mutation, the PFS benefit was very large (HR 0.10, p < 0.0001), confirming the predictive value of EGFR mutations [32]. Overall, the OS benefit was limited to patients with stable disease after first-line therapy (HR 0.72, p = 0.0019), whereas the OS benefit was not significant in patients with remission (HR 0.94, p = 0.6181) [33]. One has to bear in mind that these data rest upon a small and selected subgroup of the whole study population. In the ATLAS trial, after four cycles of platinum-based chemotherapy with bevacizumab, patients were randomized to maintenance with either bevacizumab plus erlotinib or bevacizumab alone. There was a significant improvement in PFS in favour of maintenance (HR 0.72, p = 0.0012) [34] but no improvement of OS (HR 0.90, p = 0.27) [35] (Tab. 2). The 3-arm IFCT-GFPC 0502 trial discussed above also showed a significant benefit in PFS for maintenance therapy with erlotinib after first-line therapy with cisplatin and gemcitabine (HR 0.82, p = 0.002) [16].

Ongoing clinical trials

The role of pemetrexed maintenance after first-line therapy including pemetrexed is currently tested in the PARAMOUNT trial (S124; identifier: NCT00789373). This trial is comparing maintenance pemetrexed versus placebo in non progressive patients after first-line therapy with four cycles of cisplatin and pemetrexed. ECOG 5508 (identifier: NCT01107626) is comparing pemetrexed versus bevacizumab versus pemetrexed plus bevacizumab in patients responding to carboplatin, paclitaxel and bevacizumab induction. The Pointbreak trial (NCT00762034) is testing maintenance pemetrexed plus bevacizumab after carboplatin, pemetrexed plus bevacizumab, versus bevacizumab maintenance after carboplatin, paclitaxel and bevacizumab. The Swiss Group for Clinical Cancer Research (SAKK) is conducting the SAKK19/09 trial (NCT01116219) of induction with pemetrexed, cisplatin and bevacizumab, followed by maintenance with pemetrexed and bevacizumab in patients with advanced non-squamous and EGFR wildtype NSCLC. Finally, CALGB 30607 (identifier: NCT00693992) investigates the maintenance therapy with sunitinib after four cycles of platinum-based chemotherapy.

Summary and recommendations

Clinical evidence

Based on the current evidence in 2010, there is no established benefit for continuation maintenance for patients with advanced NSCLC after first-line therapy. On the other hand, switch maintenance therapy may be a good option especially for patients with stable disease. In these patients, erlotinib and pemetrexed are two valid options. Pemetrexed is active only in non-squamous NSCLC and is established only if pemetrexed has not been given in first-line therapy [15, 23]. However, based on the trial by Scagliotti and Gandara, pemetrexed in combination with cisplatin is nowadays a widely used first-line therapy [24]. For patients receiving pemetrexed in the first-line setting, erlotinib maintenance is a good option. Erlotinib maintenance is approved irrespective of tumour histology. Patients with activating EGFR mutations who did not receive an EGFR-inhibitor in the first-line should be treated with gefitinib or erlotinib early after induction chemotherapy. As discussed above, there are still some reasons to hold on to an interval without therapy especially in patients with good response to the first-line chemotherapy. In this case it is crucial to closely monitor the patient.

Approval status as of 2010

The EMEA approved pemetrexed for the maintenance treatment for non progressive patients with non-squamous histologies after platinum-based chemotherapy in combination with gemcitabine, paclitaxel or docetaxel. Swissmedic licensed pemetrexed in a broader patient population, as the first-line therapy is only defined to be platinum-based. Maintenance treatment with erlotinib is approved for patients with stable disease after four cycles of standard platinum-based first-line chemotherapy by the EMEA. Swissmedic approved erlotinib for all patients with locally advanced or metastatic NSCLC progressive after one prior chemotherapy.

Conflicts of interest

SIR: none.

OG is chairing an investigator-initiated clinical trial supported by Roche and Eli Lilly.

### Tab. 2: Overview on clinical phase III trials studying switch maintenance therapy with EGFR tyrosine kinase inhibitors

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>1st-line therapy</th>
<th>Maintenance therapy</th>
<th>PFS [mo]</th>
<th>OS [mo]</th>
</tr>
</thead>
<tbody>
<tr>
<td>WJTOG0203 [30]</td>
<td>604</td>
<td>Platinum-doublet (×3)</td>
<td>Chemotherapy cont. (×3) vs. Gefitinib</td>
<td>4.3 vs. 4.6*</td>
<td>12.9 vs. 13.7</td>
</tr>
<tr>
<td>EORTC 08021 – ILCP 01/03 [31]</td>
<td>173</td>
<td>Platinum-doublet (×2–6)</td>
<td>Gefitinib vs. placebo</td>
<td>4.1 vs. 2.9*</td>
<td>10.9 vs. 9.4</td>
</tr>
<tr>
<td>SATURN [32]</td>
<td>889</td>
<td>Platinum-doublet (×4)</td>
<td>Erlotinib vs. placebo</td>
<td>12.3 vs. 11.1 weeks (HR 0.71)*</td>
<td>12 vs. 11 months (HR 0.81)*</td>
</tr>
<tr>
<td>ATLAS [34, 35]</td>
<td>768</td>
<td>Platinum-doublet + Beva (×4)</td>
<td>Beva + Erlotinib vs. Beva</td>
<td>5.7 vs. 2.7*</td>
<td>15.9 vs. 13.9</td>
</tr>
</tbody>
</table>

Beva bevacizumab, *p < 0.05.
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tabine with cisplatin plus pemetrexed in chemotherapy-naive pati-


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