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REVIEW

The Effectiveness of Maintenance Pharmacotherapies for Non-Small Cell Lung Cancer

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Abstract: Although current recommendations for the treatment of advanced non-small cell lung cancer (NSCLC) include a maximum of six cycles of platinum-based combination therapy as a first-line approach, most patients experience progression within 3–4 months. Therefore, a new treatment strategy, maintenance therapy, has been proposed, and several large randomized prospective controlled trials have shown benefits with maintenance therapy. Maintenance therapy can be classified as either continuation maintenance, which is defined as a prolongation of a part of the first-line chemotherapy or molecularly targeted agent until progression, or switch-maintenance, which is defined as the administration of a different cytotoxic chemotherapy or molecularly targeted agent immediately after induction therapy. In this article, recent results from large randomized phase III trials regarding maintenance therapy are reviewed in order to evaluate the role of maintenance therapy in NSCLC.

Keywords: non-small cell lung cancer, maintenance therapy

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Introduction

Lung cancer is the leading cause of cancer death worldwide.[1] Non-small cell lung cancer (NSCLC) accounts for 80% of lung cancer diagnoses, and the majority of patients with NSCLC present with locally advanced or metastatic disease. Platinum-based doublet chemotherapy has been considered the gold standard for first-line pharmacotherapy for advanced NSCLC, giving rise to modest increases in survival and symptom improvement. Current guidelines by the American Society of Clinical Oncology for patients with advanced stage IV NSCLC include a maximum of six cycles of platinum-based doublets based on the results of several randomized trials and meta-analyses, demonstrating that prolonged periods of administration of platinum-based chemotherapy did not improve overall survival (OS).[2–6] Nevertheless, most patients experience progression within 3–4 months after 4–6 cycles of first-line therapy. Therefore new treatment strategies, such as maintenance therapy are needed to delay disease progression, to prevent symptom deterioration, to maintain patients' performance status to allow further therapy, and eventually to increase OS. Maintenance therapy can be classified as either continuation maintenance, which is defined as a prolongation of a part of the first-line chemotherapy or molecularly targeted agent until progression, or switch-maintenance, which is defined as the administration of a different cytotoxic chemotherapy or molecularly targeted agent immediately after induction therapy. In this article, recent results from large randomized phase III trials regarding maintenance therapy are reviewed in order to evaluate the role of maintenance therapy in NSCLC.

Materials and Methods

The following key words were used for PubMed search; non-small cell lung cancer, maintenance, chemotherapy, gefitinib, erlotinib, cetuximab, and antiagiogenic. Also the proceeding of American Society of Clinical Oncology annual meeting, the proceedings of European Society of Medical Oncology, and the proceedings of World Conferences on Lung Cancer from 2003 to 2011 were searched. Only articles written in the English language were eligible. Phase III randomized studies were preferentially selected for this review.

Continuation Maintenance Therapy

Continuation maintenance with a cytotoxic agent

Prolonged use of platinum-based doublet chemotherapy increases toxicity without survival benefit, and most patients cannot tolerate such an approach. Therefore, the continuation of non-platinum cytotoxic chemotherapy has been actively investigated in patients who achieve at least stable disease (SD) with induction therapy.

Belani et al performed a large randomized trial of paclitaxel maintenance after induction using various combinations of carboplatin and paclitaxel. Patients who responded after four cycles of induction chemotherapy were randomized to receive weekly maintenance doses of paclitaxel or best supportive care (BSC).[7] The primary endpoint of this study was time to progression (TTP). The median TTP in the paclitaxel arm was 38 weeks compared with 29 weeks in the BSC arm ($P = 0.124$) with no difference in median OS (75 vs. 60 weeks, $P = 0.243$). Of note, only 23% of patients completed four cycles of paclitaxel, and 45% experienced at least one grade 3 or 4 adverse event.

A randomized phase III multicenter trial of gemcitabine maintenance therapy after a combination of gemcitabine and cisplatin in 350 patients with advanced NSCLC was conducted by Brodowicz et al.[8] Patients who achieved at least SD were randomized in a 2:1 ratio to receive maintenance gemcitabine plus BSC or BSC alone. The primary endpoint was TTP, and the secondary endpoints included overall response rate, response duration, OS, toxicity, and symptom control. Two hundred fifteen patients were randomized to gemcitabine maintenance or BSC; finally, 138 patients were treated with gemcitabine and 68 were treated with BSC. The median TTP as the primary endpoint was significantly prolonged in the gemcitabine maintenance arm at 6.6 months compared with 5 months in the BSC group ($P < 0.001$). However, there was no difference in OS between the gemcitabine and BSC arms (13 vs. 11 months, $P = 0.195$). Although gemcitabine was well tolerated, patients receiving gemcitabine required a greater number of transfusions than the BSC group (20% vs. 6.3% $P = 0.018$).

Gemcitabine maintenance after induction of gemcitabine and carboplatin has also been reported. Of 519 patients, 128 patients with a stable or partial response were randomized to gemcitabine maintenance and 127 were randomized to BSC.[9] The primary endpoint was progression-free survival (PFS). There was no difference in PFS or OS (7.4 vs. 7.7 months for PFS; 8.0 vs. 9.3 months for OS) between the BSC and maintenance group. Patients treated with gemcitabine experienced more neutropenia (15% vs. 2%), thrombocytopenia (9% vs. 4%), and fatigue (5% vs. 2%) than those in the BSC group.

Another gemcitabine maintenance trial was conducted by a French group [Intergroupe Francophone de Cancerologie Thoracique-Groupe Francais de Pneumo-Cancerologie (IFCT-GFPC) 0502].[10] Patients who achieved at least SD with four cycles of induction chemotherapy of gemcitabine and cisplatin were randomized to observation, gemcitabine, or erlotinib. This study had a unique design in that pemetrexed as a second-line therapy was assigned to all patients. The primary endpoint of this study was PFS. An independent review demonstrated that median PFS was prolonged in the gemcitabine arm compared with the observation arm (3.8 vs. 1.9 months; hazard ratio [HR], 0.55; $P < 0.001$). Although 69.6% of events were observed at the time of analysis, the HR for OS between the gemcitabine and observation arms was 0.86 (95% CI, 0.66–1.12). However, this trial did not have sufficient statistical power for meaningful survival differences due to the small number of patients in each arm.

The PARAMOUNT study was a randomized phase III clinical trial that compared continuation maintenance with pemetrexed vs. placebo plus BSC.[11] After four cycles of pemetrexed and cisplatin as an induction therapy in 939 patients with nonsquamous cell NSCLC, 539 patients who did not progress were randomized in a 2:1 ratio to either the continuation of the single agent pemetrexed (n = 359) or BSC (n = 180). The primary endpoint was median PFS, which was significantly longer in the pemetrexed arm (3.9 months) than in the placebo arm (2.6 months) by independent review (HR = 0.64, $P = 0.0002$). The final result of OS is not available. Although patients treated with pemetrexed maintenance experienced more fatigue, anemia, and neutropenia, these toxicities were confined to less than 5% of the study population (Table 1).

Switch Maintenance Therapy

Switch maintenance with cytotoxic agents

Switch maintenance is defined as the administration of an alternative, non-cross-resistant agent, cytotoxic chemotherapy, or molecularly targeted agent immediately after induction therapy. This treatment strategy is based on the Goldie-Coldman hypothesis that even the smallest detectable cancers contain at least one drug-resistant clone and that increasing numbers of resistant clones emerge as tumors grow and progress.[12]

Westeel et al conducted a randomized trial of 573 patients with stage IIIB/IV NSCLC who were treated with mitomycin, ifosfamide, and cisplatin.[13] Among 227 patients who achieved partial response, 181 patients were randomized to receive either maintenance treatment with weekly vinorelbine for 6 months or BSC. There was no difference in either median PFS or OS between the maintenance and BSC arms (5 vs. 3 months $P = 0.32$; 12.3 vs. 12.3 months $P = 0.48$, respectively). The most common causes of premature termination of chemotherapy were progressive disease (38%) and toxicity (21%). Moreover, this study needs further validation because the role of vinorelbine as a second-line treatment has not been established.

Fidias et al performed a landmark switch maintenance therapy study that compared immediate docetaxel maintenance after completion of four cycles of induction carboplatin and gemcitabine with observation and docetaxel given at the time of progression.[14] Of 566 patients, 309 patients who achieved at least SD were randomized to either immediate or delayed docetaxel therapy. The primary endpoint was PFS, which was significantly longer for the immediate docetaxel arm than the delayed arm ($P = 0.0001$). The median OS was better in the immediate docetaxel arm than in the delayed arm (12.3 vs. 9.7 months, $P = 0.085$) without statistical significance. Of note, 94.8% of patients received at least one cycle of immediate docetaxel, whereas only 62.8% of patients in the delayed arm received docetaxel at the time of progression. The most common reasons for not administering docetaxel to patients in the delayed arm were disease

progression, patient or investigator decision, and death. However, the median OS for patients in the immediate arm was almost identical to that of patients who received docetaxel in the delayed arm (12.3 vs. 12.5 months, respectively), suggesting that whether patients are treated with a second-line therapy is more important than the maintenance therapy itself.

Ciuleanu and colleagues conducted a randomized phase III trial that compared pemetrexed maintenance with placebo (2:1 ratio) in patients who achieved at least SD after one of three platinum-based induction chemotherapy regimens.[15] Of 660 patients, 441 patients received pemetrexed maintenance, and 222 patients received placebo. The primary endpoint was PFS. There were significant differences in median PFS between the pemetrexed and placebo arms (4.3 vs. 2.6 months, HR 0.6, $P = 0.00001$). Of note, pre-specified histological subgroup analysis showed that patients with a non-squamous histology had a HR of 0.47 ($P = 0.00001$) for median PFS. Similarly, among patients with a non-squamous histology, the median OS for patients receiving pemetrexed maintenance therapy was 15.5 months vs. 10.3 months for the placebo arm (HR = 0.79, $P = 0.012$). Although 67% of patients were treated with various salvage therapies in placebo arm, the fact that only 19% of patients in placebo arm were treated with pemetrexed at the time of progression can raise doubt about the exact role of pemetrexed as maintenance therapy. Nevertheless, it is the first study to demonstrate survival benefit from switch maintenance therapy with pemetrexed in patients with non-squamous NSCLC. Based on these results, the Federal Drug Authority and The European Medicines Agency approved pemetrexed as a maintenance therapy in cases of non-squamous NSCLC (Table 2).

Switch maintenance with molecularly targeted agents

With advances in understanding lung cancer biology, several molecularly targeted agents have been developed and approved for the treatment of NSCLC, such as anti-angiogenic agents that target vascular endothelial growth factor (VEGF), bevacizumab, small molecule epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) (gefitinib or erlotinib), and anti-EGFR monoclonal antibody (cetuximab). Due to their low toxicities, these agents have been investigated as maintenance therapies. Earlier trials of combinations of platinum doublets with bevacizumab or cetuximab showed survival benefit, but these molecularly targeted agents were incorporated in both the induction and maintenance phases.[16,17] However, the definitive role of maintenance therapy with a single use of a molecularly targeted agent has not yet been established. Here, only maintenance treatment trials with molecularly targeted agents after induction of platinum doublets will be reviewed.

Previous trials with concurrent treatments of gefitinib or erlotinib combined with platinum doublets did not show any survival benefit compared with standard platinum doublets.[18–21] However, the survival benefit in a subset of patients who were maintained with EGFR TKIs prompted investigators to investigate the role of EGFR TKIs as a maintenance therapy.

The first landmark study, the sequential Tarceva in unresectable non-small cell lung cancer trial (SATURN) was conducted.[22] 889 patients who did not progress during the four cycles of platinum doublets were randomized to receive either maintenance erlotinib or placebo. Patients were stratified by EGFR expression, as determined by immunohistochemistry, and EGFR gene copy number, as determined by fluorescence in situ hybridization. The primary endpoint was PFS. With erlotinib maintenance, there was a significant prolongation of both median PFS and OS (HR = 0.71, $P < 0.0001$ and HR = 0.81, $P = 0.0088$, respectively). However, no significant interactions, as determined by biomarkers such as EGFR expression or EGFR gene copy number, were observed. In contrast, a significant PFS benefit from erlotinib was observed in patients with EGFR mutations in exon 19 or 21 compared with those patients with wild-type EGFR. The HR was 0.1 ($P < 0.0001$), which was remarkable. There was no difference in OS in these groups of patients due to crossover to erlotinib when progression occurred. Although 72% of patients in the placebo arm received salvage therapy, only 21% of patients crossed over to erlotinib. Of note, survival benefit was seen even in patients with wild-type EGFR. However, survival benefit was only confined to patients who achieved SD compared with those patients who achieved a partial response. Based on these data, erlotinib was approved by The European Medicines Agency only in patients who achieve SD after induction therapy.

Table 1. Summary of randomized clinical trials of continuation maintenance therapies.

Study/year	Induction therapy	Maintenance therapy	Medain TTF/PFS	Median OS	Grade ¾ toxicity
North American Study[7] 2003	Carboplatin/paclitaxel for 16 weeks Arm 1: paclitaxel 100 mg/m^2 weekly for 3 of 4 weeks with carboplatin AUC 6 on day 1 Arm 2: paclitaxel 100 mg/m^2 and carboplatin AUC 2 weekly for 3 of 4 weeks Arm 3: paclitaxel 150 mg/m^2 cycle 1 and 100 mg/m^2 cycle 2 and carboplatin AUC 2 weekly for 6 of 8 weeks (n = 401)	Paclitaxel 70 mg/m^2 weekly (n = 65) Observation (n = 65)	38 wk 29 wk	75 wk 60 wk	45% for paclitaxel arm
Central European Cooperative Oncology Group[8] 2006	Gemcitabine 1250 mg/m^2 D1D8/cisplatin 80 mg/m^2 D1 q 3 wks × 4 cycles (n = 352)	Gemcitabine 1250 mg/m^2 D1 D8 q 3 wks (n = 138) BSC (n = 68) (2;1 randomized)	6.6 m 5.0 m $P < 0.01$	13 m 11 m	ANC 14.9%; Thrombocytopenia 1.7%; Blood transfusion 20%
POI-01-003-050[9] 2010	Gemcitabine 1000 mg/m^2 D1 D8/carboplatin AUC 5 D1 q 3 wks × 4 cycles (n = 519)	Gemcitabine 1000 mg/m^2 D1 D8 q 3 wks (n = 128) BSC (n = 127)	7.4 m 7.7 m $P = 0.575$	8.0 m 9.3 m	ANC 15% vs. 2%; Thrombocytopenia 9% vs. 4%; Fatigue 5% vs. 2%
IFCT-GFPC (French Study)[10] 2010	Gemcitabine 1250 mg/m^2 D1 D8/cisplatin 80 mg/m^2 D1 q 3 wks × 4 cycles (n = 834)	Gemcitabine 1250 mg/m^2 D1 D8 q 3 wks (n = 155) BSC (n = 155)	3.8 m 1.9 m $P < 0.001$	NR NR	27.9% vs. 2.6%
PARAMOUNT[11] 2011	Pemetrexed 500 mg/^{2} D1/cisplatin 75 mg/m^2 D1 q 3 wks × 4 cycles (n = 539)	Pemetrexed 500 mg/m^2 D1 q 3 wks (n = 359) BSC (n = 180)	3.9 m 2.6 m $P < 0.0002$	NR NR	9.2% vs. 0.6% Fatigue 4.2% vs. 0.6 Anemia 4.5 vs. 0.6 Neutropenia 3.6 vs. 0.6

Abbreviations: ANC, absolute neutrophil count; wk, week; NR, not reported.

Table 2. Summary of randomized clinical trials of switch maintenance therapies.

Study/year	Induction therapy	Maintenance therapy	N	Median PFS	Salvage therapy (%)	Median OS
GCOT (French study)[13] 2005	MIC × 4 +/– RT (Mitomycin C 6/mgm^2 D1, ifosfamide 1.5 g/m^2 D1-3, cisplatin 30 mg/m^2 D-3 q 3 wks × 4 cycles or 2 cycles of MIC + 60 Gy RT)	Vinorelbine 25 mg/m^2 weekly Observation	573	5.0 m 3.0 m HR = 0.77 $P = 0.11$		12.3 m 12.3 m HR = 1.08 $P = 0.65$
Fidias et al[14] 2008	Carboplatin AUC 5/Gemcitabine 1000 mg/m^2 D1D8 q 3 wks × 4 cycles	Immediate docetaxel 75 mg/m^2 q 3 wks Delayed docetaxel 75 mg/m^2 q 3 wks	309	5.7 m 2.7 m HR = 0.63 $P < 0.001$	63	12.3 m 9.7 m HR = 0.80 $P = 0.085$
JMEN[15] 2009	Platinum-based × 4 cycles (gemcitabine, docetaxel or taxol + cisplatin or carboplatin)	Pemetrexed 500 mg/m^2 D1 q 3 weeks Placebo	663	4.0 m 2.0 m HR = 0.60 $P < 0.001$ HR = 0.44 (4.5 m vs. 2.6 m)*	51 67 (18% pem)	13.4 m 10.6 m HR = 0.79 $P = 0.012$ HR = 0.7 (15.5 m vs. 10.3 m)*
SATURN[22] 2009	Platinum-based doublets × 4 cycles	Erlotinib 150 mg/day Placebo	889	12.3 wk 11.1 wk HR = 0.71 $P < 0.001$	71 72 (21% EGFR TKI)	12.0 m 11.0 m HR = 0.81 $P = 0.0088$
ATLAS[23] 2010	Platinum-based + bevacizumab 15 mg/kg × 4 cycles	Erlotinib 150 mg/day + Bevacizumab 15 mg/kg Placebo + Bevacizumab 15 mg/kg	768	4.8 m 3.8 m HR = 0.72 $P = 0.0012$	55.5	15.9 m 13.9 m HR = 0.9 $P = 0.268$
IFCT-GFPC[10] 2010	Cisplatin 80 mg/m^2 D1/gemcitabine 1250 mg/m^2 D1 D8 × 4 cycles	Erlotinib 150 mg/day Observation	310	2.9 m 1.9 m HR = 0.82 $P = 0.002$	63 76	Not available Not available HR = 0.91
INFORM[25] 2010	Platinum based doublets × 4 cycles	Gefitinib 250 mg/day Placebo	296	4.8 m 2.6 m HR = 0.42 $P < 0.0001$	58.8	18.7 m 16.9 m HR = 0.83 $P = 0.210$

Note: *for non-squamous NSCLC.
Abbreviation: NA, not available.

In the ATLAS study, 743 patients who did not progress after four cycles of induction treatment with paclitaxel/carboplatin/bevacizumab were randomized to receive either bevacizumab/erlotinib or bevacizumab/placebo.[23] The primary end point of PFS was met with a HR of 0.72 ($P < 0.001$). However, the difference in median PFS between the two arms was only 1 month. The follow-up results showed no differences in median OS.

As part of a switch maintenance study conducted by a French group (Intergroupe Francophone de Cancerologie Thoracique-Groupe Francais de Pneumo-Cancerologie [IFCT-GFPC] 0502), patients who achieved at least SD with four cycles of an induction chemotherapy of gemcitabine and cisplatin were randomized to observation, gemcitabine, or erlotinib.[10] All patients were assigned to pemetrexed as a second-line therapy at the time of progression. Independent review demonstrated that the median PFS was prolonged in the erlotinib arm compared with the observation arm (2.9 vs. 1.9 months, HR = 0.82, $P = 0.002$).[10]

For locally advanced stage III NSCLC, the Southwest Oncology Group 0023 trial was conducted.[24] Patients who were treated with concurrent chemoradiotherapy followed by consolidation docetaxel were randomized to receive either maintenance gefitinib or placebo. However, this trial was also closed early due to lack of response and high mortality in the gefitinib arm by the data and safety monitoring committee.

Recently, a gefitinib maintenance trial in advanced NSCLC cases was conducted by Chinese investigators. Patients who achieved at least SD with four cycles of platinum-based chemotherapy were randomized to receive either gefitinib (n = 148) or placebo (n = 148).[25] The primary endpoint was PFS. Patients treated with gefitinib showed prolonged median PFS compared with placebo (4.8 vs. 2.6 months, HR = 0.42, $P < 0.0001$). Biomarker analysis demonstrated dramatic differences in median PFS according to EGFR mutation status. Patients treated with gefitinib maintenance showed significant prolongation of median PFS compared with placebo (HR = 0.17), whereas no differences were noted in patients with wild-type EGFR (HR = 0.86). (Table 2)

Angiogenesis is another important target for the treatment of NSCLC; thus, many different kinds of anti-angiogenic molecularly targeted agents have been investigated to improve clinical outcomes of patients with NSCLC. Bevacizumab, a monoclonal antibody directed against VEGF, was the first anti-angiogenic agent to demonstrate OS when combined with carboplatin/paclitaxel compared with carboplatin/paclitaxel alone.[17] Although no survival benefit was observed in the Avail study, the median PFS was prolonged with the addition of bevacizumab to the combination of gemcitabine and cisplatin.[26] In both studies, bevacizumab was administered as both induction and maintenance chemotherapies, making it difficult to evaluate the exact role of bevacizumab as a maintenance treatment. Since then, a number of small molecule angiogenic inhibitors that target VEGF have been investigated in combination with platinum-doublets.[27–31] Unfortunately, these studies did not show any survival benefit compared with standard combination chemotherapy.[27–31] Recently, vandetanib, a dual blocker of EGFR and VEGF TKIs, as a maintenance therapy was studied in patients who achieved at least SD after induction chemotherapy with gemcitabine and cisplatin.[32] In this double blind, placebo-controlled phase II study, vandetanib at a dose of 300 mg/day was administered only in the maintenance phase. The primary endpoint was PFS at 3 months. The intention to treat (ITT) analysis included 117 patients (75 in the vandetanib arm and 42 in the placebo arm). A pre-planned interim analysis showed that PFS at 3 months was 29% with placebo, leading to the termination of this arm, whereas PFS at 3 months in the vandetanib arm was 37.5%, allowing the second stage to proceed for this arm. The final ITT analysis, including second stage, demonstrated 37.3% of PFS at 3 months for the vandetanib arm.

Discussion

Given that most patients experience disease progression within 3–4 months after 4–6 cycles of first-line chemotherapy, maintenance therapy as a new treatment strategy would be a reasonable approach. In the trial of Fidias et al,[14] only 67% of patients were able to receive second-line therapy at the time of progression even with intensive follow-up, suggesting that patients who progress rapidly do not have an opportunity to receive salvage therapy. This finding might provide a rationale for maintenance treatment. At present, cumulative data from large randomized clinical trials of maintenance

therapy and meta-analyses have demonstrated that maintenance therapies show prolongation of PFS and improvement of OS.[33] However, it does not appear that maintenance treatments can be applied to all NSCLC patients. Therefore, there exists a patient population that can benefit from maintenance therapy, whereas there is a patient population that does not need maintenance therapy and can enjoy a drug holiday. No biomarker is available to select a patient population that may benefit from maintenance treatment. We retrospectively analyzed NSCLC patients who had achieved non-progression after four cycles of platinum doublets and were off therapy, but could not receive second-line therapy at the time of progression.[34] Among 271 patients, 39 (14.4%) patients had not received second-line therapy, primarily due to the rapid progression of disease in the lung, brain or bone metastases, or patient refusal. Multivariate analysis showed that a smaller decrease in target lesions after first-line therapy, a greater than 7-cm length of the target lesion, and poor PS are all associated with not receiving second-line therapy, suggesting that maintenance therapy might be beneficial for those patients.

Regarding maintenance therapy, several factors should be considered. Whether switch maintenance is better than continuation maintenance remains controversial. Recent meta-analyses from eight trials consisting of 3,736 patients demonstrated that clinically substantial and statistically significant improvements in PFS were observed with both maintenance strategies; HR = 0.53 from continuation maintenance and HR = 0.67 from switch maintenance.[33] Additionally, switch maintenance therapy substantially improved OS compared with placebo or observation (HR = 0.85, $P < 0.001$). A similar trend of improved OS was observed in continuation maintenance therapy without statistical significance (HR = 0.88, $P = 0.124$). At present, subgroup analyses revealed no statistically significant differences in OS or PFS between switch maintenance therapies with cytotoxic agents or EGFR TKIs.

Performance status is another important issue regarding maintenance therapy, especially continuation maintenance. Of two trials that evaluated gemcitabine maintenance, clinical benefit was only seen in the French trial, not in the trial from Belani et al, in which 64% of patients with PS2 were enrolled compared with only 6% of patients in the French study, suggesting that patients with poor PS might not benefit from maintenance therapy.

Response status to induction chemotherapy might affect the benefit received from maintenance therapy. It appears that patients who achieved a partial response had more benefit from continuation maintenance than those with SD. On the other hand, patients who achieved SD might benefit more from switch maintenance therapy.

In terms of histology, the JMEN study demonstrated survival benefit only in non-squamous NSCLC patients who were treated with pemetrexed,[15] which is consistent with previous studies.[35] However, survival benefit was seen in both adenocarcinoma and squamous histologies for erlotinib maintenance in the SATURN study.[22]

The East-Asian subgroup analysis showed that maintenance pemetrexed and erlotinib improved PFS after first-line treatment but did not show definite OS benefit. This finding might be attributed to a higher proportion of patients who received post-study treatment.[36] However, one should cautiously interpret these data due to insufficient statistical power. Therefore, to avoid effects of EGFR mutation dilution, future clinical trials of maintenance therapies with EGFR TKIs are needed in NSCLC patients with wild-type EGFR.

Quality of life (QOL) is another important issue, especially in NSCLC patients who have limited life expectancy. Although several studies have addressed this issue,[8,14,22] no definitive improvement of QOL with maintenance therapy was reported, although it was not reported to have deteriorated.

Not all patients benefit from maintenance therapy. Therefore, further research is warranted to develop biomarkers for patient selection regarding who may benefit from maintenance therapy. Given the high cost of molecularly targeted agents, an evaluation of cost-effectiveness is also needed.

Author Contributions

Conceived and designed the experiments: MJ Ahn. Analysed the data: JM Sun, Jin Sock Ahn, Keunchil Park and MJ Ahn. Wrote the first draft of the manuscript: MJ Ahn. Contributed to the writing of the manuscript: JM Sun, Jin Sock Ahn, Keunchil Park. Agree with manuscript results and conclusions:

JM Sun, Jin Sock Ahn, Keunchil Park. Jointly developed the structure and arguments for the paper: JM Sun, Keunchil Park. Made critical revisions and approved final version: JM Sun, Keunchil Park. All authors reviewed and approved of the final manuscript.

Competing Interests

Authors disclose no potential conflicts of interest.

Disclosures and Ethics

As a requirement of publication author(s) have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest. Provenance: the authors were invited to submit this paper.

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