December 23rd, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: ESPS Manuscript NO 7346-edited Maintaining Clarity Review of maintenance therapy in non small cell lung cancer.doc).

Title: Maintaining Clarity: Review of maintenance therapy in non-small cell lung cancer

Author: Kristen R. Dearing, Ashish Sangal, Glen J. Weiss

Name of Journal: *World Journal of Clinical Oncology*

ESPS Manuscript NO: 7346

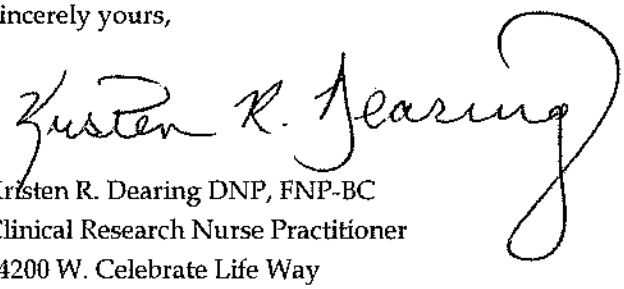
The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer
(1) "PointBreak study" p=8, line 7
(2) Patel JD, Socinski MA, Garon EB, et al. PointBreak: a randomized phase III study of pemetrexed plus carboplatin and bevacizumab followed by maintenance pemetrexed and bevacizumab versus paclitaxel plus carboplatin and bevacizumab followed by maintenance bevacizumab in patients with stage IIIB or IV nonsquamous non-small-cell lung cancer. J Clin Oncol 2013; 31: 4349-4357

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Clinical Oncology*.

Sincerely yours,



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December 23rd, 2013

Lian-Sheng Ma, President and Company Editor-in-Chief
BPG CORPORATE HEADQUARTERS
World Journal of Clinical Oncology

Dear Editor-in-Chief,

We are submitting the invited review article entitled, "Maintaining Clarity: Review of maintenance therapy in non-small cell lung cancer" for consideration to be published in the World Journal of Clinical Oncology. The purpose of this article is to review the role of maintenance therapy in the treatment of advanced non-small cell lung cancer (NSCLC). The development of how maintenance therapy is utilized in this population is discussed and current guidelines for maintenance therapy are reviewed. Benefits and potential pitfalls of maintenance therapy are addressed, allowing a comprehensive review of the achieved clinical benefit that maintenance therapy may or may not have on NSCLC patient population. We believe that this will be of great interest and raise awareness for clinical oncologists taking care of patients with advanced NSCLC.

As noted in the invitation—"There is no restriction on number of words, figures, tables and references. Your paper will be published free of charge after peer review."

Thank you for your consideration.

Sincerely,

Kristen R. Dearing, DNP, FNP-BC on behalf of all authors
Cancer Treatment Centers of America

World Journal of Clinical Oncology
ESPS Manuscript NO: 7346

Maintaining Clarity: Review of maintenance therapy in non-small cell lung cancer

Dearing KR *et al*. Maintaining Clarity: Review of maintenance therapy in non-small cell lung cancer

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Abstract

The purpose of this article is to review the role of maintenance therapy in the treatment of advanced non-small cell lung cancer (NSCLC). A brief overview about induction chemotherapy and its primary function in NSCLC is provided to address the basis of maintenance therapies foundation. The development of how maintenance therapy is utilized in this population is discussed and current guidelines for maintenance therapy are reviewed. Benefits and potential pitfalls of maintenance therapy are addressed, allowing a comprehensive review of the achieved clinical benefit that maintenance therapy may or may not have on NSCLC patient population. A review of current literature was conducted and a table is provided comparing the results of various maintenance therapy clinical trials. The table includes geographical location of each study, the number of patients enrolled, progression free survival (PFS) and overall survival (OS) statistics, post-treatment regimens and if molecular testing was conducted. The role of molecular testing in relation to therapeutic treatment options for advanced NSCLC patients is discussed. A treatment algorithm clearly depicts first line and second line treatment for management of NSCLC and includes molecular testing, maintenance therapy and the role clinical trials have in treatment of NSCLC. This treatment algorithm has been specifically tailored and developed to assist clinicians in the management of advanced NSCLC.

Key Words: maintenance therapy; clinical trials; non-small cell lung cancer; molecular mutations; progression-free survival; overall survival

Core Tip: This review article addresses the role of maintenance therapy in the treatment of advanced non-small cell lung cancer (NSCLC). Maintenance therapy utilization in NSCLC patient population and review of current guidelines for maintenance therapy are discussed. A treatment algorithm was created to depict first line and second line treatment for managing NSCLC and includes molecular testing, maintenance therapy, and the role of clinical trials in the treatment of NSCLC. A comprehensive review of the achieved clinical benefit that maintenance therapy may or may not have on the NSCLC patient population is presented.

Dearing KR, Sangal A, Weiss GJ. Maintaining Clarity: Review of maintenance therapy in non-small lung cancer. World J Clin Oncol 2013;
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Current first-line therapy management of advanced NSCLC

Lung cancer remains one of the leading causes of cancer-related death in men and women worldwide and attributes approximately 1.37 million deaths per year worldwide.[1]Non-small cell lung cancer (NSCLC) is the most common form of lung cancer and approximately 2/3 of patients with NSCLC present with advanced disease.[2] This advanced disease state leads to limited treatment options, [3] primarily systemic therapy. According to NCCN (National Comprehensive Cancer Network) guidelines, 4-6 cycles of platinum-based doublet chemotherapy is recommend as first-line treatment in patients without a driver mutation, such as, EGFR (epidermal growth factor receptor) mutation or ALK (anaplastic lymphoma kinase) rearrangement.[4] For those patients with an EGFR mutation or ALK rearrangement, use of a specific inhibitor directed at that target is indicated either as the initial treatment or as therapy when progressive disease develops.

The platinum doublet generally consists of cisplatin or carboplatin with another cytotoxic agent, sometimes in combination with a biologic agent such as bevacizumab. Multiple cytotoxic agents in addition to cisplatin and carboplatin have antitumor activity in NSCLC. These include pemetrexed, taxanes (docetaxel, paclitaxel, nanoparticle albumin bound paclitaxel), gemcitabine, vinorelbine, and camptothecins (irinotecan, topotecan). The use of cytotoxic chemotherapy as the initial treatment for patients not selected based upon EGFR mutation status and for those whose tumors do not contain an EGFR mutation is supported by the results of the TORCH trial.[5] In that trial, 760 patients were randomly assigned to either first-line erlotinib followed by chemotherapy (cisplatin plus gemcitabine) upon progression or the same first-line chemotherapy followed by erlotinib upon progression. Overall survival (OS) was significantly longer in unselected patients assigned to initial chemotherapy followed by second-line erlotinib (median 11.6 versus 8.7 months, hazard ratio [HR] 1.24, 95% CI 1.04-1.47). For patients known to be EGFR mutation negative, OS was significantly longer with initial chemotherapy (median 9.6 versus 6.5 months). Combination chemotherapy regimens using a platinum doublet result in median OS of 8-11 months.[3]

Evaluation of the Role of Maintenance Therapy

Extending the duration of treatment with the initial platinum based chemotherapy beyond four to six cycles has been evaluated. Currently, there is little evidence to support continuous doublet cytotoxic chemotherapy after 4-6 cycles being given until disease progression,[6] although longer treatment duration increases progression-free survival (PFS), it has at most only a modest effect on OS.[7] Maintenance therapy

is an extension of induction chemotherapy and is continued for a determined period of time unless there is disease progression or significant toxicities develop.[8] The goal is to extend a favorable patient response from first-line platinum based combination chemotherapy.[9] There are two types of maintenance therapy, known as continuation and switch maintenance therapy. Continuation maintenance therapy is the administration of one chemotherapy agent that was part of the initial chemotherapy regimen. Continuation maintenance therapy can involve either a non-platinum cytotoxic drug or a molecular targeted agent. Switch maintenance therapy, involves administration of a new chemotherapy agent that was not part of the original chemotherapy regimen and a potentially non-cross-resistant agent that is started immediately after completion of first-line induction chemotherapy.[9] Currently, switch-maintenance therapy with pemetrexed or erlotinib is FDA-approved. With the standard 4-6 cycles of platinum based chemotherapy, patients may have a response within the first 2-4 cycles; however, many patients cannot tolerate long-term treatment.[10] Disease progression and co-morbidities that arise due to disease progression contribute to the intolerance of long-term treatment.

Historically, treatment for advanced NSCLC involved waiting until disease progression before a second-line therapy was started.[8] After first-line therapy, "drug holidays" rarely lasting more than 3 months in duration can pose a risk for rapid clinical deterioration leading to ineligibility for second-line treatment.[11,12] This led to clinical trials investigating the role for maintenance therapy using 3rd generation cytotoxic agents and targeted therapy.[8] Many of these studies either did not have adequate power to detect statistical significance for survival benefits or did not have a placebo control arm.[8]

Advocates of maintenance therapy point to potential merits including: higher probability that tumor will be exposed to effective therapies, decreased development of chemotherapy resistance, maximizing the efficacy of chemotherapy, potentiating the anti-angiogenic effects of chemotherapy, and enhancing anti-tumor immunostimulation.[9] Many patients do not go on to receive second-line therapy due to rapid progression of disease, decrease in their performance status, or increase cancer-related symptoms. By treating patients with maintenance therapy, the window of opportunity for treatment may be extended.[3] Those patients that benefit from maintenance therapy have better performance status and responded to first-line therapy.[9]

Critics of maintenance therapy argue that the trials evaluating maintenance therapy have: inconsistent clinical trial endpoints, impose a detrimental effect on quality of life, prevent some patients from having a drug holiday, add increased associated costs,[9] and eliminate from the armamentarium standard second-line chemotherapy agents if they are used as maintenance therapy. Patients on maintenance chemotherapy with stable disease may also be exposed to additional toxicities[6] although some maintenance therapies like pemetrexed have limited grade 3-4 toxicities, such as fatigue and neutropenia,[8] and may be better tolerated.

There are currently five medications that are U.S. Food and Drug Administration (FDA) approved for maintenance therapy in NSCLC (bevacizumab, cetuximab, pemetrexed, gemcitabine, and erlotinib).[4] Data exist on some agents that perform better or worse based on tumor histology. For example, regimens containing pemetrexed are more effective in patients with adenocarcinoma and have not demonstrated a meaningful clinical benefit for patients with squamous cell carcinoma. The impact of histology was illustrated by a phase III trial in which cisplatin plus pemetrexed was compared with cisplatin plus gemcitabine as initial therapy.[13,14] Survival in the 847 patients with adenocarcinoma was significantly prolonged with cisplatin plus pemetrexed compared to cisplatin plus gemcitabine (median 12.6 vs.10.9 months, p=0.03). Conversely, cisplatin plus gemcitabine was superior to cisplatin plus pemetrexed in the 473 patients with squamous cell carcinoma (median 10.8 vs. 9.4 months, p=0.05). Ultimately, the outcome from this study and review of previous trial data led to the re-labeling of pemetrexed for use in non-squamous NSCLC.

Review of Maintenance Therapy Trials

A list with pertinent details of large randomized maintenance therapy trials in NSCLC is provided in **Table 1**.

In a study published in 2005, vinorelbine 25mg/m2 was evaluated as a maintenance therapy given weekly for 6 months until disease progression compared with observation alone in stage IIIB/IV NSCLC patients after induction with MIC treatment (mitomycin 6mg/m2, ifosfamide 1.5mg/m2, cisplatin 30mg/m2 given every four weeks x 2-4 cycles +/- radiotherapy).[15] A total of 91 patients were randomized to vinorelbine maintenance therapy. Median PFS for vinorelbine was 5 months vs. 3 months with observation, but the difference was not statistically significant. Median OS for both groups were the same at 12.3 months and evaluation of molecular subtypes were not performed.

A phase III trial evaluating continuation maintenance therapy with gemcitabine 1250mg/m2 every 3 weeks until disease progression or request for removal vs. best supportive care (BSC) was reported.[2] Advanced NSCLC patients were given gemcitabine 1250mg/m2 and cisplatin 80mg/m2 every 3 weeks for 4 cycles as an induction regimen. Two hundred six patients were given gemcitabine while 138 patients received BSC alone. Median time to progression from induction was measured and was a median of 6.6 months with gemcitabine vs. 5 months with BSC ($p<0.001$, Hazard ratio [HR] 0.7; 95% confidence interval [CI], 0.5-0.9). Median OS from induction for gemcitabine was 13 months compared to 11 months, but not significantly different (p=0.195). Karnofsky performance status (KPS) was taken into consideration with OS and patients were split into KPS > 80 versus KPS ≤ to 80. Patients with KPS > 80 had a HR 2.1 of dying while on gemcitabine and patients with KPS ≤ to 80 had HR 0.8. Using continuation maintenance therapy with gemcitabine after induction with gemcitabine and cisplatin did

demonstrate a longer time to progression (TTP) vs. BSC for patients with advanced NSCLC. No molecular testing was conducted in this study.

The ECOG 4599 study evaluated the effectiveness of bevacizumab (B) maintenance therapy in patients with advanced NSCLC nonsquamous histology only.[16] Patients completed carboplatin 6mg/ml AUC and paclitaxel 200mg/m2 induction chemotherapy every three weeks for six cycles or carboplatin 6mg/ml AUC, paclitaxel 200mg/m2 and B 15mg/kg every three weeks for six cycles. Patients were randomized to B 15mg/kg maintenance therapy or surveillance (only patients without progressive disease after induction therapy were eligible for this arm). Median PFS was significantly higher for B vs. surveillance at 6.2 months vs. 4.5 months ($p<0.001$). Median OS was significantly higher for B vs. surveillance at 12.3 months vs. 10.3 months ($p=0.003$). No tumor molecular testing was completed for this study.

In 2009, the JMEN study, an international randomized, double-blind, phase III study of maintenance pemetrexed with BSC vs. placebo plus BSC for NSCLC resulted in pemetrexed being approved by the FDA for use as maintenance therapy in NSCLC.[10] Patients were treated with one of six induction regimens (gemcitabine-carboplatin, gemcitabine-cisplatin, paclitaxel-carboplatin, paclitaxel-cisplatin, docetaxel-carboplatin or docetaxel-cisplatin) every 3 weeks for four cycles. Patients were assigned randomized 2:1 to receive pemetrexed 500mg/m2 or placebo. Median PFS plus induction was 7.7 months for pemetrexed vs. 5.9 months for placebo ($p<0.0001$, HR 0.50; 95% CI 0.42-0.61). Median OS plus induction was 16.5 months with pemetrexed vs. 13.9 months with placebo ($p=0.012$, HR 0.79; 95% CI, 0.65-0.95). Overall, switch maintenance therapy with pemetrexed demonstrated improved PFS and OS and was well-tolerated. In this study, no tumor tissue molecular testing was conducted.

In a phase III study of advanced NSCLC patients receiving induction therapy with gemcitabine 1000mg/m2 and carboplatin AUC= 5 every 21 days for four cycles, patients that did not demonstrate disease progression were randomized to immediate docetaxel 75mg/m2 every 21 days for six cycles or were given docetaxel with the same dosage and schedule once they presented with disease progression.[12] Immediate administration of docetaxel maintenance therapy demonstrated a statistically significant increase in median PFS compared with delayed docetaxel (5.7 months vs. 2.7 months, $p=0.001$). Median OS was not statistically significant for either arm of the study and no molecular testing on patients' tumors was completed.

The "PointBreak" study randomized advanced NSCLC patients to pemetrexed 500mg/m2, carboplatin AUC = 6, B 15mg/kg induction every 21 days with four cycles, with maintenance pemetrexed 500mg/m2, B 15mg/kg (PB) versus paclitaxel 200mg/m2, carboplatin AUC = 6, B 15mg/kg induction every 21 days for four cycles, with maintenance B 15mg/kg.[17,18] The maintenance therapy for both arms was given until disease progression. Median PFS was significantly higher for PB vs. B at 6 months versus

5.6 months, respectively (p=0.012, HR 0.83; 95% CI, 0.7-0.96). Median OS was not significantly different for PB vs. B at 12.6 months vs. 13.4 months, respectively. The primary endpoint of improved median OS was not met. While tumor molecular testing was conducted, the types of testing and results have not been reported.

The FLEX study, randomized previously untreated advanced NSCLC patients to cisplatin 80mg/m2 plus vinorelbine 25mg/m2 every 3 weeks for six cycles, with or without cetuximab 400mg/m2 day 1 and 250mg/m2 day 8 and all subsequent doses weekly.[19] Cetuximab maintenance was given until disease progression/toxicities. Median PFS was not statistically significant (p=0.39, HR 0.94; CI, 0.82-1.07). Median OS for cetuximab vs. observation was 11.3 months vs. 10.1 months (p= 0.044, HR 0.87; CI, 0.76-0.99). Tumor molecular testing was conducted for EGFR immunohistochemistry and was part of the entry criteria for study eligibility.

The AVAIL study, randomized advanced NSCLC patients to cisplatin 80mg/m2 plus gemcitabine 1250mg/m2 every three weeks for six cycles, with either B (7.5 mg/kg), B (15 mg/kg), or placebo every three weeks until disease progression.[20] Median PFS for low dose B vs. placebo was 6.7 months vs. 6.1 months (p=0.003, HR 0.75; CI, 0.62-0.91). Median PFS for high dose B vs. placebo was 6.5 months vs. 6.1 months (p=0.03, HR 0.82; CI, 0.68-0.98). Median OS was not analyzed due to insufficient follow-up duration at the time of data reporting. Overall, B as maintenance therapy does improve PFS. No tumor molecular testing was conducted.

The SATURN study evaluated erlotinib as maintenance therapy in advanced NSCLC patients who received one of seven different platinum based doublet chemotherapy regimens (type of regimens were not specified).[3] Induction therapy was given for four cycles followed by erlotinib 150mg/day vs. placebo until disease progression, toxicity, or death. No B or pemetrexed were used in the induction chemotherapy regimens. Median PFS for erlotinib vs. placebo was significantly prolonged at 4.1 months vs. 2.75 months, respectively (p<0.0001, HR 0.69; 95% CI, 0.58-0.82). Median OS with erlotinib vs. placebo was also significantly improved at 12 months vs. 11 months (p=0.0088, HR 0.81; 95% CI, 0.70-0.95). From this trial, molecular testing of EGFR immunohistochemistry was reported.

The BMS-099 study, randomized advanced NSCLC patients to carboplatin AUC = 6 plus either docetaxel 75 mg/m2 or paclitaxel 225mg/m2 every three weeks for six cycles or carboplatin AUC = 6 plus either docetaxel 75mg/m2 or paclitaxel 225mg/m2 every three weeks for six cycles with cetuximab 400 mg/m2 day 1, 250mg/m2 day 8 and each subsequent dose.[21] Cetuximab was given weekly until disease progression/toxicities. Median PFS and OS were not statistically significant. Maintenance cetuximab added no clinical benefit to PFS or OS. No tumor molecular testing was included in this study.

The PARAMOUNT study evaluated the use of pemetrexed as continuation maintenance therapy in patients with advanced NSCLC nonsquamous histology.[22,23] Patients were given pemetrexed

500mg/m2 and cisplatin 75mg/m2 every three weeks for four cycles. Patients were then randomized to pemetrexed 500mg/m2 continuation maintenance every three weeks until disease progression or placebo. Median PFS was significantly higher for pemetrexed maintenance vs. placebo at 4.1 months vs. 2.8 months, respectively ($p<0.0001$, HR 0.62; 95% CI, 0.49-0.79). Median OS was significantly higher for pemetrexed maintenance vs. placebo at 13.9 months vs. 11 months, respectively ($p=0.0195$, HR 0.78; 95% CI, 0.64-0.96). The use of pemetrexed as continuation maintenance therapy can significantly increase median PFS and OS in patients with advanced nonsquamous NSCLC. No tumor molecular testing was conducted.

The IFCT-GFPC 0502 study evaluated gemcitabine (continuation maintenance) vs. erlotinib (switch maintenance) vs. observation as maintenance therapy after induction therapy with cisplatin 80mg/m2 and gemcitabine 1250mg/m2 every three weeks for four cycles in patients with advanced NSCLC.[11] Patients were then randomized to gemcitabine 1250mg/m2 every three weeks, erlotinib 150mg/day every three weeks, or observation until disease progression, toxicity, or death. Median PFS for gemcitabine vs. erlotinib vs. observation was 3.8 months ($p<0.001$, HR 0.56; 95% CI 0.44-0.72) vs. 2.9 months ($p=0.003$, HR 0.69; 95% CI 0.54-0.88) vs. 1.9 months. Median OS was not significantly different for gemcitabine vs. erlotinib vs. observation at 12.1 months vs. 11.4 months vs. 10.8 months; respectively. Molecular testing was completed for EGFR IHC (n =261) and EGFR mutation (n=188). Fourteen different EGFR mutations were noted (exon 19 deletion (n=10), exon 21(n=4)). EGFR IHC had no significant effect on median PFS for gemcitabine or erlotinib therapy and there were too few cases of EGFR mutations for analysis.

The AVAPREL study evaluated the use of B with or without pemetrexed as maintenance therapy in advanced NSCLC with nonsquamous histology with B 7.5mg/kg, cisplatin 75mg/m2 and pemetrexed 500mg/m2 every three weeks for four cycles as induction chemotherapy regimen.[24] Patients were randomized to B 7.5mg/kg alone or B 7.5mg/kg plus pemetrexed 500mg/m2 (PB) given every three weeks until disease progression/toxicities. Median PFS for PB vs. B was 7.4 months vs. 3.7 months ($p<0.001$, HR 0.48; 95% CI, 0.35-0.66). Median OS was not significantly different between the two arms. No tumor molecular testing was completed in this study.

Molecular Analysis and Its Impact on Maintenance Therapy

Therapy for advanced NSCLC should be individualized based upon the molecular features of the tumor. Whenever possible, tumor tissue should be assessed for the presence of a somatic driver abnormality (e.g., mutated EGFR, ALK rearrangement) which confers sensitivity to a specific inhibitor.[25] Unfortunately, many clinical trials do not require collection of tumor tissue for molecular analysis as either entry criteria or for subsequent analysis. There are no randomized trials conducted in patients

known to have an EGFR mutation or other driver abnormality prior to the initiation of maintenance chemotherapy. After review of maintenance therapy trials cited here, three of 10 had molecular subtypes identified and two of these three trials had pre-planned analysis for molecular subtype EGFR mutations. Furthermore, structuring of clinical trials that identify patients with molecular alterations and evaluating their response to standard maintenance therapy has been minimal.[26] An improved understanding of the molecular pathways that drive malignancy in NSCLC has led to the development of agents that target specific molecular pathways in malignant cells. These agents have been a significant step forward in the treatment of patients whose tumors contain specific mutations in these pathways. Most patients with advanced NSCLC whose tumors contain a driver mutation are initially treated with the appropriate targeted agent (e.g., erlotinib, gefitinib, or crizotinib). For patients with advanced NSCLC who were initially treated with chemotherapy but in whom a driver mutation has subsequently been identified, continuation of therapy with an appropriate targeted agent after the initial cycles of chemotherapy are complete is recommended.[3]

By taking into consideration patient demographics and obtaining molecular testing target treatment plans can be made. EGFR mutations and ALK rearrangements are more common in NSCLC tumors of patients that have a history of never to light smoking, compared to KRAS (Kirsten rat sarcoma viral oncogene homolog) mutations which are often found in tumors of heavy smokers.[27] Treatment with EGFR tyrosine kinase inhibitors (TKIs) (such as erlotinib, gefitinib, or afatinib) as single agents is indicated for the initial management of patients whose tumors contain an activating mutation in EGFR. In this setting, first-line treatment with an EGFR TKI improves PFS compared to standard platinum-based chemotherapy. The impact on OS is less clear, since EGFR TKIs were frequently used as second line therapy after chemotherapy in the clinical trials demonstrating the efficacy of this approach. EGFR TKIs generally are not combined with platinum-based doublet chemotherapy as initial therapy, since these combinations have not prolonged survival even when patients were selected for sensitivity to these EGFR TKIs based upon clinical criteria. In the absence of significant toxicity, treatment with an EGFR TKI is continued until there is evidence of progression. An example of second-line therapy that has been shown to be more effective in a specific patient population is pemetrexed and ALK rearranged tumors. ALK-positive tumors have a significant response to pemetrexed leading to longer PFS when compared to KRAS mutant, EGFR mutant, or triple negative tumors in patients treated with pemetrexed.[27] Information on molecular subtypes should be considered.[26] Pemetrexed is cost effective for patients with non-squamous cell histology and shows the importance in identifying patients who will benefit from pemetrexed maintenance therapy.[8]

Crizotinib, an inhibitor of the ALK tyrosine kinase, is preferred as first-line therapy in patients whose tumor contains the ALK fusion oncogene. Phase II studies using crizotinib demonstrated an

objective response rate over 50 percent in previously treated patients with ALK rearrangements, with a median duration of response greater than 40 weeks in responders. A phase III trial demonstrated a significant increase in PFS compared to standard chemotherapy in patients who had previously received one platinum-containing regimen.[28] Further development and research can help distinguish if ALK-positive tumors are responsive to cytotoxic agents or specifically responsive to pemetrexed alone. Such findings can improve the way NSCLC patients with distinct tumor molecular phenotypes are treated and how these treatments can impact outcomes.[27]

Discussion

The role of maintenance treatment for patients with advanced NSCLC is under active investigation. There are several factors to consider when choosing to start a patient on maintenance therapy. These factors include deciding how and whether to continue therapy including patient's tolerance for these agents, absence or presence of molecular mutations, patient specific factors like co-morbidities, toxicity associated with the original treatment, and desire to balance clinical benefit versus toxicity of immediate further treatment. The studies reviewed have shown that maintenance therapy could provide clinical benefit in specific advanced NSCLC patients. However, as alluded to earlier, few features that can help identify those most likely to benefit from maintenance therapy have been identified.

Not all advanced NSCLC lung cancer patients are made equal and continuation maintenance therapy to date may improve OS in first-line therapy responders,[11] whereas switch maintenance therapy, can improve OS in patients with stable disease after first-line therapy.[29] More research into identifying factors that contribute to response rate of various maintenance therapies would allow for better selection of patients to receive maintenance therapy.[26] A recent study identified patients who normally were not qualifying candidates based on common clinical trial inclusion guidelines (such as socioeconomically disadvantaged and patients with greater symptom burden requiring pre-chemotherapy palliative radiation therapy), and observed that this subset of patients maintained stable disease after first line chemotherapy without additional therapy and at time of disease progression responded well to second-line chemotherapy. This is an example of how some patients may benefit successfully without the use of maintenance therapy.[30] Identification of these factors will assist providers to better define patient populations who should receive maintenance chemotherapy and decrease costs and toxicities in patients who may or may not benefit from having maintenance chemotherapy.

Measurement of PFS and OS should not be the only factors determining the success of maintenance therapy. Patient perspectives need to be taken into consideration. PFS is valued if disease symptoms are minimal, but these gains can be offset as disease symptoms progress or toxicity burden from treatment impacts that patient.[30] Clinical benefit is an important determinant in deciding if patients are candidates for maintenance therapy. By identifying patients' goals and their tolerance of adverse symptoms, determination about the appropriate use of maintenance therapy can be made.

An additional factor when determining the utilization of maintenance therapy is cost effectiveness of maintenance therapy, which can vary depending on location. For example, maintenance pemetrexed is more cost effective compared to other maintenance therapies in the United Kingdom, but is not cost effective in the United States (U.S.).[30] Identification of those patients who will gain the greatest benefit from maintenance therapy will help balance efficacy, cost, and patient preferences.

Several of the studies displayed statistically significant results for primary or secondary endpoint PFS. Although PFS was prolonged in many studies, the concern of 'statistical significance' in relation to clinical significance needs attention by the critical eye of a clinician. A result that is statistically significant does not mean that the result is clinically significant and vice versa.[31] Historically and currently, the trend for reporting and interpreting clinical trial results are not based on the prospect of clinical importance.[32] When interpreting clinical trial results, the p-value is not the only 'value' indicating that the study was statistically significant. The number of subjects in the study contributes largely to reaching a statistically significant number, but not a clinically significant result.[31] For example, a study with a very large number of subjects commonly will show significant p-values but overall, the clinical significance and treatment differences are very small.[31]

There have been four maintenance studies to date reporting statistically significant improved PFS and OS. Three out of the four studies, ECOG4599, JMEN, and PARAMOUNT, did not report tumor molecular analysis. The former study involved B maintenance and the latter two studies involved pemetrexed maintenance. The fourth study, SATURN, did evaluate patient tumors for EGFR mutation retrospectively, however, those with EGFR mutations had the most dramatic "benefit" of significantly prolonged PFS and OS.[3] Unfortunately, the majority of maintenance studies reviewed did not conduct molecular testing. To accurately measure the clinical benefit of maintenance therapy in advanced NSCLC patients, their molecular tumor analysis or prospective sample collection should be included as criteria for future clinical trials. As discussed above, the question of clinical versus statistical significance is important to point out with all four of these studies. All were very large study populations (at least 663 subjects each) and while the primary results demonstrated statistically significant improvements in median OS, the reality is these are not blockbuster changes for clinically meaningful improvement over standard platinum based doublet therapy in exchange for potential increased treatment-related toxicity and financial-related toxicity.

Other considerations to take into account for maintenance therapy as more oral biologic agents come to the clinic, is patient adherence with their prescribed anticancer therapy. Adherence to treatment is a major factor that can impact outcomes, though the quality of data on this topic and interventions to improve adherence need improvement as well.[33]

Precision-based oncology care allows treatment of advanced NSCLC to be personalized to the patient not the cancer. Just as TKIs have been incorporated into standard of care for treatment of patients with specific tumor molecular mutations,[4] TKIs and metabolic inhibitors have and may continue to demonstrate more significant prolongation of PFS and OS in patients with molecular mutations. As oncologists and advanced practitioners create treatment plans for advanced NSCLC patients, testing for molecular mutations is crucial for selecting the right treatment and stratifying how best to treat patients

eligible for systemic therapy. A suggested algorithm for treating stage 4 NSCLC is outlined in **Figure 1**. By taking histology and molecular subtypes into consideration, more succinct and clear identification of patients that would benefit from one maintenance therapy agent versus other alternatives is likely important. Molecular subtypes may behave differently to various standard therapies resulting in the need for developing of targeted therapies for patients with NSCLC.[27] More advancement is needed in treating NSCLC patients that do not display molecular mutations.[9] By recognizing these new developments as well as limitations, there is a need for clinicians to be able to identify patients who will have the greatest benefit and effectiveness from maintenance therapy.

Legend to Figure 1. Treatment Algorithm

Stage 4 nonsquamous NSCLC should have their tumors analyzed for EGFR, KRAS, ALK, and ROS1 in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory setting. For patients with EGFR mutation, we recommend first-line therapy is erlotinib or afatinib or a clinical trial. For patients with ALK or ROS1 rearrangements, we recommend first-line crizotinib therapy. We recommend continuation of targeted therapy until disease progression. Upon disease progression, provided the patient is eligible to receive additional therapy, we next recommend a clinical trial or platinum-doublet systemic chemotherapy for 4-6 cycles with or without bevacizumab (drug holiday). Upon disease progression, provided the patient is eligible to receive additional therapy, we next recommend a clinical trial or another NCCN guideline recommended cytotoxic therapy.

For patients with squamous, KRAS mutation, or wild-type for these 4 molecular phenotypes, we recommend platinum-doublet systemic chemotherapy for 4-6 cycles with or without bevacizumab or a clinical trial. Note: bevacizumab should not be administered to patients with squamous cell carcinoma. Those patients with stable disease or better can proceed on maintenance therapy or have a drug holiday. Those with disease progression on first-line therapy or developing disease progression during maintenance therapy or drug holiday, can be evaluated for a clinical trial or another NCCN guideline recommended cytotoxic therapy, provided the patient is eligible to receive additional therapy.

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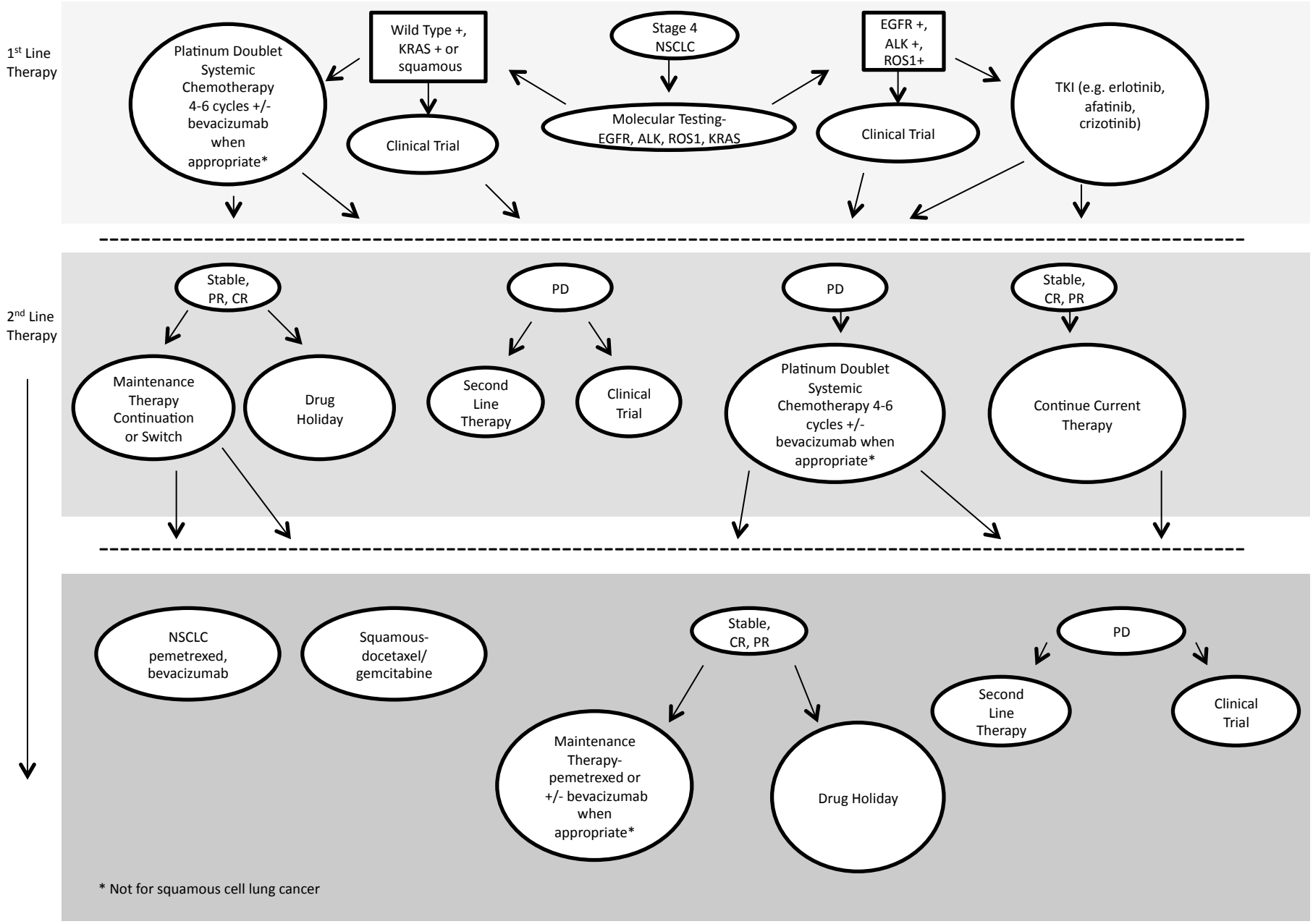
Study	Location	Tumor Type	N enrolled=	Induction		N= enrolled	Maintenance		PFS	HR	P value	CI 95%
Vinorelbine Maintenance [15]	France	NSCLC	566	Mitomycin 6mg/m2 q4w Ifosfamide 1.5g/m2 q4w Cisplatin 30mg/m2 q4w	Stage IIIB= x2 cycles + XRT Stage IIIB+ pleural/pericardial/supraclavicular involvement or IV= x4 cycles	91 vs. 90	Vinorelbine 25mg/m2 qweekly vs. Observation	x6m until PD	5.0m 3.0m	0.77	p=0.11	0.56-1.07
Cis/Gem w/ Gem Maintenance[2]	Europe	NSCLC	352	Gemcitabine 1250mg/m2 q21days Cisplatin 80mg/m2 q21days	x 4 cycles	138 vs. 68	Gemcitabine 1250mg/m2 q21days vs. BSC	until PD/removal request	3.6m (TTP) 2.0m (TTP)	0.7	p<0.001	0.5-0.9
ECOG 4599[16]	United States	NS-NSCLC	878	Carboplatin AUC 6mg/ml q3w Paclitaxel 200mg/m2 q3w vs. Carboplatin AUC=6mg/ml q3w Paclitaxel 200mg/m2 q3w	x 6 cycles x 6 cycles	434 vs. 444	Bevacizumab 15mg/kg q3w vs. Observation	until PD	6.2m 4.5m	0.66	p<0.001	0.57-0.77
JMEN[10]	20 countries	NSCLC	663	Gemcitabine-Carboplatin q21days Gemcitabine-Cisplatin q21days Paclitaxel-Carboplatin q21days Paclitaxel-Cisplatin q21days Docetaxel-Carboplatin q21days Docetaxel-Cisplatin q21days	x 4 cycles	441 vs. 222	Pemetrexed 500mg/m2 q21days vs. Placebo	until PD	4.3m 2.6m	0.5	p<0.0001	0.42-0.61
Docetaxel Maintenance[12]	United States	NSCLC	566	Gemcitabine 1000mg/m2 q21days Carboplatin AUC 5 q21days	x 4 cycles	153 vs. 156	Immediate Docetaxel 75mg/m2 q21days vs. Delayed Docetaxel 75mg/m2 (start at PD) q21days	x 6 cycles	5.7m 2.7m	NR	p=0.0001	2.6-2.9m
POINTBREAK[17,18]	United States	NS-NSCLC	939	Pemetrexed 500mg/m2 q21days Carboplatin AUC 6 q21days Bevacizumab 15mg/kg q21days vs. Paclitaxel 200mg/m2 q21days Carboplatin AUC 6 q21days Bevacizumab 15mg/kg q21days	x 4 cycles x 4 cycles	292 vs. 298	Pemetrexed 500mg/kg + Bevacizumab 15mg/kg q21days vs. Bevacizumab 15mg/kg q21days	until PD or discontinued until PD or discontinued	6.0m 5.6m	0.83	p=0.012	0.7-0.96
FLEX[19]	International	NSCLC	1125	Cisplatin 80mg/m2 q3w Vinorelbine 25mg/m2 q3w Cetuxamab 400mg/m2 day 1, 250mg/m2 day 8 & subsequent doses qweekly vs. Cisplatin 80mg/m2 q3w Vinorelbine 25mg/m2 q3w	x 6 cycles x 6 cycles	557 vs. 568	Cetuxamab 250mg/m2 weekly Observation	until PD/toxicities	4.8m 4.8m	0.94	p=0.39	0.82-1.07
AVAIL[20]	20 countries	NS-NSCLC	1043	Cisplatin 80mg/m2 q3w Gemcitabine 1250mg/m2 q3w	x 6 cycles	345 vs 351 vs 347	Bevacizumab 7.5mg/m2 vs. Bevacizumab 15mg/m2 vs. Placebo	until PD	6.7m 6.5m 6.1m	0.75 0.82	p=0.003 p=0.03	
SATURN[3]	26 countries	NSCLC	1949	Platinum Doublet Chemotherapy (7 different regimens-not reported) No Bevacizumab/Pemetrexed Allowed	x 4 cycles	438 vs. 451	Erlotinib 150mg/day vs. Placebo	until PD/toxicities/death	4.1m 2.75m	0.71	p<0.0001	0.62-0.82
BMS- 099[21]	United States	NSCLC	676	Paclitaxel 225mg/m2 q3w or Docetaxel 75mg/m2 q3w Cetuximab 400 mg/m2 day 1, 250 mg/m2 day 8 & subsequent doses qweekly vs. Paclitaxel 225mg/m2 q3w or Docetaxel 75mg/m2 q3w Carboplatin AUC 6 q3w	x 6 cycles	325 vs 320	Cetuximab 250mg/m2 weekly Observation	until PD/toxicities	4.4m 4.2m	0.9	p=0.236	0.76-1.06
PARAMOUNT[22,23]	Europe	NS-NSCLC	939	Pemetrexed 500mg/m2 q3w Cisplatin 75mg/m2 q3w	x 4 cycles	359 vs. 180	Pemetrexed 500mg/m2 q3w vs. Placebo	until PD	4.1m 2.8m	0.62	p<0.0001	0.49-0.79
IFCT-GFPC 0502[11]	France	NSCLC	834	Cisplatin 80mg/m2 q3w Gemcitabine 1250mg/m2 q3w	x 4 cycles	154 vs. 155 vs. 155	Gemcitabine 1250mg/m2 q3w vs. Erlotinib 150mg/day q3w vs. Observation	until PD/toxicity/death until PD/toxicity/death 	3.8m 2.9m 1.9m	0.56 0.69	p<0.001 p=0.003	0.44-0.72 0.54-0.88
AVAPREL[24]	Europe	NS-NSCLC	376	Bevacizumab 7.5mg/kg q3w Cisplatin 75mg/m2 q3w Pemetrexed 500mg/m2 q3w	x 4 cycles	125 vs. 128	Pemetrexed 500mg/kg + Bevacizumab 7.5mg/kg q3w vs. Bevacizumab 7.5mg/m2 q3w	until PD until PD	7.4m 3.7m	0.48	p<0.001	0.35-0.66

*NS-NSCLC: Nonsquamous Non-Small Cell Lung Cancer

PFS + Induction	HR	P value	CI 95%	OS	HR	P value	CI 95%	OS + Induction	HR	P value	CI 95%	Genotype	Post-TX
NR				12.3m				NR				Not Collected	Etoposide 80mg/m2, Cisplatin 30mg/m2
NR	NR	NR	NR	12.3m		1.08 p=0.65		NR	NR	NR	NR		
6.6m (TTP+Induction)				10.2m				13m				Not Collected	Second Line Chemotherapy/ Radiation
5.0m (TTP+ Induction)		0.7 p<0.001	0.5-0.9	8.1m		p=0.172		11m	NR	p=0.195			
NR	NR	NR	NR	12.3m		0.79 p=0.003	0.67-0.92	NR	NR	NR			
NR				10.3m				NR				Not Collected	None Reported
7.7m				13.4m				16.5m				Not Collected	Pemetrexed, Docetaxel, Erlotinib, Gefitinib, Vinorelbine, Gemcitabine, Carboplatin, Cisplatin, Paclitaxel
5.9m		0.5 p<0.0001	0.42-0.61	10.6m		0.79 p=0.012	0.65-0.95	13.9m		0.79 p=0.012	0.65-0.95		
NR				12.3m				NR	NR			Not Collected	Best Supportive Care, Observed for PD/Survival
NR	NR	NR	NR	9.7m	NR	p=0.853		NR	NR	NR	NR		
8.6m				12.6m				17.7m	NR			Collected-No specific results	None Reported
6.9m	NR	NR	NR	13.4m		1 p=0.949		15.7m	NR	NR	NR		
NR	NR	NR	NR	11.3m		0.87 p=0.044	0.76-0.99	NR	NR	NR	NR	Collected- EGFR (IHC)	None Reported
				10.1m									
NR	NR	NR	NR	Not Sufficient				NR	NR	NR	NR	None Collected	No Bevacizumab
NR	NR			12m				NR	NR			EGFR/Wild Type/Resistance Mutations	Erlotinib (people in placebo group that were EGFR +, Taxanes (+docetaxel), Antimetabolics (+ pemetrexed), Platinums, Antineoplastics
NR	NR	NR	NR	11m		0.81 p=0.0088	0.70-0.95	NR	NR	NR	NR		
NR	NR	NR	NR	9.6m		0.89 p=0.169	0.75-1.05	NR	NR	NR	NR	Not included in study	None Reported
				8.3m									
6.9m				13.9m				16.9m				Not Collected	Erlotinib, Docetaxel, Gemcitabine, Vinorelbine, Cisplatin, Bevacizumab, Investigational Drug
5.6m		0.59 p<0.0001	0.47-0.74	11.0m		0.78 p=0.0195	0.64-0.96	14.0m		0.78 p=0.0191	0.64-0.96		
NR				12.1m		0.89 p=0.3867		15.2m		0.72 NS		EGFR Mutations/Expressions (exon 19 deletions, mutations in exon 21 and L858R point mutations)	Pemetrexed 500mg/m2 q21days, Erlotinib, Docetaxel
NR				11.4m		0.87 p=0.3043		NR	NR				
NR				10.8m				10.8m					
10.2m		0.5 p<0.001	0.37-0.69	NR		0.75 p=0.219	0.47-1.19	NR		0.75 p<.23	0.47-1.20	Not Collected	Taxanes/TKI
6.6m				12.8m				15.7m					

Treatment Algorithm



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