Published in final edited form as:
Drugs. 2013 May ; 73(6): 517–532. doi:10.1007/s40265-013-0032-4.

Re-examination of maintenance therapy in non-small cell lung cancer with the advent of new anti-cancer agents

Eamon M. Berge and **Robert C. Doebele**
Department of Medicine, Division of Medical Oncology, University of Colorado, Aurora, CO

Abstract

Metastatic non-small cell lung cancer (NSCLC) remains a disease with a high annual incidence and annual mortality worldwide, with limitations in first line treatment past a fixed amount of platinum doublet chemotherapy for patients that do not harbor a targetable genetic abnormality such as an *EGFR* mutation or *ALK* gene rearrangement. Previous attempts to extend first line treatment past four to six cycles of conventional cytotoxic chemotherapy have been disappointing, resulting in diminished quality of life and increased toxicity without improvement of progression free or overall survival. Several advances in third generation chemotherapy and targeted agents have generated a renewed interest in maintenance therapy, with several randomized phase III trials reporting a significant improvement in progression free and overall survival with manageable toxicity profiles. The availability of new chemotherapy agents, tyrosine kinase inhibitors, and immunotherapy agents with a more tolerable or nonoverlapping toxicity profile have resulted in improvement in progression free survival and median overall survival in maintenance settings with specific agents such as pemetrexed and erlotinib. Patients who are responding to first line therapy, have not suffered a detrimental decrease in quality of life or performance status, and that understand the risks and benefits of further immediate chemotherapy should be considered for maintenance treatment.

Keywords

NSCLC; Maintenance; Lung Cancer

Introduction

Non-small cell lung cancer (NSCLC) remains one of the most commonly diagnosed and lethal malignancies, accounting for 15 to 17% of new cancer diagnoses, of which 56% are metastatic at the time of diagnosis.[1-3] Despite recent advances in therapy and different treatment approaches based on histologic molecular subtypes, initial chemotherapy with a platinum doublet remains standard of care for patients with metastatic disease that do not harbor a targetable mutation.[4] A standard approach is to employ a “watch and wait” approach after completion of 4-6 cycles of first line chemotherapy and is advocated by

Corresponding Author: Eamon M. Berge, MD, Mail Stop 8117, 12801 E. 17th Avenue, Room 8105, Aurora, CO 80045, Ph: 303-724-3847 Fax: 303-724-3889 Eamon.Berge@ucdenver.edu.

Berge, EM: No conflict of interest to disclose

multiple guidelines;[5-7] however this approach is often met with anxiety by patients and providers. Recent breakthroughs in tyrosine kinase inhibitors (TKI) for metastatic NSCLC that harbors epidermal growth factor receptor (*EGFR*) mutations or anaplastic lymphoma kinase (*ALK*) rearrangements have rekindled the desire to offer safe, tolerable continuation of therapy to all NSCLC patients, as these agents are commonly administered with no fixed cycle length and are discontinued only when progression or unacceptable toxicity occurs.[8-10] Furthermore, while there are now several viable second line therapeutic options, only approximately 50-60% of patients in retrospective reviews and clinical trials receive second line therapy, most often due to declining performance status.[11-14] These concerns have led to multiple attempts to extend the number of cycles given prior to progression – an approach typically referred to as "maintenance" therapy. Until recently, there has been little high level clinical evidence to justify routine use of maintenance therapy.

Maintenance strategies in NSCLC are generally categorized as either "continuous" or "switch". Continuous maintenance is defined as continued administration of one or more drugs in the first line setting past 4-6 cycles until progressive disease or limiting toxicity. Switch maintenance is defined as consecutive administration of second line chemotherapeutic agents after completion of 4-6 cycles of first line chemotherapy. For the purpose of this article, relevant phase II and phase III studies were identified by searching PubMed and Embase up to October 2012 without language restriction. The search was performed by using keywords "NSCLC," "non-small-cell lung cancer," "maintenance," "consolidation," and "early second-line." This search was supplemented by a manual search of the annual meeting proceedings of the American Society of Clinical Oncology. Key phase III studies and meta-analyses that address the role of maintenance treatment of patients with NSCLC were cross-referenced in order to identify all relevant trials. The aim of this review is to provide an historical perspective into how maintenance strategies have evolved, review the most recent data addressing maintenance therapy in NSCLC, and identify clinical trials in process, with particular emphasis on larger phase III trials that offer comparison of maintenance therapy to best supportive care or placebo arms.

Continuation Maintenance Therapy

Continuation Maintenance: Conventional Chemotherapy

The concept of continuation maintenance was evaluated in its earliest forms when defining established parameters for the duration of therapy in the first line setting, and was initially evaluated comparing two different predetermined cycle numbers. The first of such trials was conducted before platinum doublet therapy was established as the standard of care, randomizing stage IIIB/IV NSCLC patients to 3 versus (vs.) 6 cycles of mitomycin, vinblastine and cisplatin (MVP).[15] In this study of 308 patients, the study failed to demonstrated a statistically significant improvement in 6 vs. 3 cycles of therapy: median time to disease progression (TTP) was 5 months in each arm with median overall survival (OS) of 6 months in the 3 cycle arm vs. 7 months in the 6 cycle arm (p=0.2). Notably, only 31% of patients randomized to the 6 cycle arm were able to complete the scheduled course of therapy, with significant incremental increases of grade 3/4 hematologic and non-

hematologic toxicities in the 6 cycle arm. Quality of life (QoL) parameters did not differ between the two groups during the initial phase of treatment but began to diverge after 9 weeks of therapy, with a significant difference in fatigue (p=0.03) and a trend toward increased grade 3 neutropenia (p=0.06) in the 6 cycle arm. Von Plessen et al. investigated treatment of IIIB/ IV NSCLC with 3 vs. 6 cycles of carboplatin plus vinorelbine with primary endpoints of OS and QoL.[16] Again, there was a non-significant trend towards improvement in median OS of 28 versus 32 weeks (p=0.75) and median progression free survival (PFS) of 16 vs. 21 weeks (p=0.21) in the 3 vs. 6 arm cycle with no significant difference in QoL parameters. 78% of patients completed 3 cycles compared to 54% patients completing 6 cycles.

Treatment duration with modern platinum doublet chemotherapy regimens was addressed by Park et al., who conducted a phase III trial designed to determine if increasing the amount of predefined cycles translated into a clinical benefit.[17] Patients who demonstrated disease control, defined as stable disease (SD), partial response (PR), or complete response (CR) by computed tomography (CT) scan, following 2 cycles of cisplatin plus paclitaxel, docetaxel or gemcitabine chemotherapy were randomized to 2 or 4 additional cycles of chemotherapy with the same agents. The trial met its primary endpoint of noninferiority between the 2 arms with a median TTP of 6.2 months with 6 total chemotherapy cycles compared with 4.6 months for 4 cycles (p=0.0001). There was no statistically significant difference in OS, with a median duration if 14.9 months in the 4 cycle arm and 15.9 months in the six cycle arm (p=0.461). A higher percentage of patients in the 4 cycle arm compared to the 6 cycle arm (74.4% vs. 62.7%; p=0.026) were able to proceed to second line therapy providing a potential reason why TTP differences did not translate into OS benefit in this trial. While QoL parameters were not directly addressed in this study, hematologic and non-hematologic treatment related adverse events (AEs) were similar between the two groups.

Continuation maintenance of a platinum doublet until disease progression was first investigated by Socinski et al., who randomized patients to 4 cycles of carboplatin plus paclitaxel every three weeks vs. continuation of doublet therapy until disease progression or toxicity with co-primary endpoints of OS and QoL.[18] Both cohorts received second line single agent paclitaxel at the time of radiographic progression and. 42% of patients in the continuation arm received greater than 4 cycles with only 45% of patients proceeding to second line therapy. There was no statistically significant difference in OS between the two arms, 6.6 months in non-continuation arm and 8.5 months in the continuation arm (p=0.63), with similar overall response rate (ORR) of 22% vs. 24% (p=0.80). There were no statistical differences in QoL measurements, and while rates of hematologic toxicity were similar, the rate of grade 2 or greater neuropathy increased from 19.9% at the 4th cycle of treatment to 43% by cycle 8. In summary, these trials evaluating continuation of chemotherapy with modern platinum-based doublets[16-18] or older regimens[15] have frequently demonstrated increased toxicity without significant clinical benefits in OS, PFS, and QoL parameters that have in part led to consensus guidelines restricting platinum doublet chemotherapy to 4 to 6 cycles.[5, 6, 19]

More recent continuation maintenance trials employing platinum doublets have investigated limiting the platinum based agent to the more conventional 4 to 6 cycles and continuation of

the non-platinum agent until progression or dose limiting toxicity. Several earlier trials were designed to allow for continuation of single agent gemcitabine after initial gemcitabine plus platinum first line therapy. Brodowicz et al. performed a phase III trial where 352 patients were randomized (2:1) after 4 cycles of cisplatin plus gemcitabine first line therapy to gemcitabine continuation vs. best supportive care (BSC) with a primary endpoint of TTP.[20] TTP favored the gemcitabine arm (6.6 vs. 5 months; $p < 0.001$) which again did not translate into a median OS difference (13.0 months for continuation gemcitabine vs. 11.0 months for BSC arms; p=0.195). A similar percentage of patients (56.6% vs. 57.1%) went on to receive second line therapy in the two arms. Belani et al. enrolled 519 patients in a phase III trial where NSCLC patients receiving first line carboplatin plus gemcitabine were randomized 1:1 to gemcitabine vs. BSC with a primary endpoint of OS. [21] There was no significant difference in median PFS between the two groups (3.9 months for gemcitabine vs. 3.8 months for BSC; p=0.575), with no statistically significant difference in median OS (9.3 months for gemcitabine vs. 8.0 months for BSC; p=0.838; HR=0.97; 95% CI: 0.72-1.30). There was a higher incidence of grade 3/4 hematologic toxicity (anemia 9.4% vs. 2.4%; neutropenia 13.3% vs. 1.6%; thrombocytopenia 9.4% vs. 1.4%) and non-hematologic (fatigue 3.9% vs. 1.6%) toxicity in the maintenance gemcitabine arm. Perol et al. conducted a phase III trial that randomized 464 NSCLC patients without progressive disease after 4 cycles of gemcitabine and cisplatin first line therapy in a 1:1:1 fashion to maintenance gemcitabine, erlotinib, or BSC with a primary endpoint of PFS. Median PFS was 3.8, 2.9, and 1.9 in the gemcitabine, erlotinib, and BSC arm, respectively. PFS in both the gemcitabine (HR=0.56; 95% CI 0.44-0.72; $p<0.001$) and erlotinib (HR=0.69; 95% CI 0.54-0.88; p=0.003) continuation maintenance were statistically significant when compared to BSC. Again, no significant median OS benefit (12.1 vs. 10.8 months; p=0.3867) was seen for gemcitabine maintenance with a 25% absolute increase in grade 3/4 treatment related AEs over observation alone (27.9% vs. 2.6%, respectively). Importantly, second line therapy with pemetrexed was pre-specified and high proportion of patients on each arm received this therapy (BSC, 90.9%; gemcitabine, 77.2%; erlotinib, 79.9%). Given the lack of any identified differences in OS, gemcitabine does not currently have Federal Drug Administration (FDA) or European Medicines Agency (EMA) approval for maintenance therapy in NSCLC.

To date, there have been two studies that have evaluated paclitaxel continuation maintenance after first line carboplatin plus paclitaxel, both published by Belani et al.[22, 23] In the first study, 309 patients were treated with three different carboplatin/paclitaxel regimens for 16 weeks total. 130 responding patients after 16 weeks of therapy were randomized (1:1) to weekly paclitaxel or observation with a primary endpoint of TTP. Although underpowered, there was a trend towards an increase in TTP with weekly paclitaxel (38 weeks) vs. observation (29 weeks). There was also a trend towards OS in the weekly paclitaxel arm (75 weeks) vs. observation (60 weeks). An additional phase III trial by the same lead author randomized 444 patients at the time of treatment initiation to 4 cycles of carboplatin/weekly paclitaxel regimen vs. 4 cycles of carboplatin/paclitaxel administered every 3 weeks with a primary endpoint of OS. Patients with SD or response (n=141) were eligible to continue treatment with weekly paclitaxel until disease progression. TTP was 33 weeks in the weekly paclitaxel arm, 29 weeks in the every 3 weeks paclitaxel

arm, compared to 11 and 12 weeks, respectively, for patients ineligible for (n=261) or that opted not to receive (n=42) maintenance therapy. There was no formal BSC or placebo arm for the maintenance portion of this trial, with approximately 70% of patients in each arm receiving maintenance chemotherapy. It is also important to note that both of the trials mentioned above were designed to compare efficacy and safety of the different weekly paclitaxel regimens and were not specifically designed to address the efficacy of continuation maintenance paclitaxel, as neither trial was sufficiently powered to detect a difference in maintenance therapy or were randomized at the start of maintenance therapy.

Pemetrexed is currently FDA and EMA approved for maintenance therapy as “switch” maintenance therapy, and is currently restricted to patients with nonsquamous histology. The histology restriction is partly based upon this agent's differential efficacy in nonsquamous histology as originally demonstrated in phase III registration trials[14, 24] with particular efficacy in patients with adenocarcinoma histology.[25] The drug's role in continuation maintenance therapy has been studied in the PARAMOUNT trial by Paz-Arez, et al.[26] 539 Patients with nonsquamous histology were randomized (2:1) after stable disease or response to 4 cycles of cisplatin and pemetrexed to continuation of pemetrexed every 3 weeks until disease progression or BSC plus placebo with a primary endpoint of PFS and secondary endpoints of patient reported outcomes, resource use, response rate, and OS.[26, 27] All patients received supplementary vitamin B12 injections, folic acid, and dexamethasone. Patients on pemetrexed continuation maintenance (n=359) had a significant improvement in PFS of 4.1 months as compared to 2.8 months (HR=0.60; 95% CI 0.5-0.73; p<0.0001). Grade 3/4 treatment related AEs were higher in the pemetrexed group when compared to the placebo, with the most common being fatigue (4.7% vs. 1.1%; p< 0.05), anemia (6.4% vs. 0.6%; p<0.05) and neutropenia (5.8% vs. 0%; p<0.05). Preplanned analysis assessing the duration of pemetrexed continuation maintenance therapy (> 6 cycles vs. < 6 cycles) demonstrated no difference in amount and severity of grade 3/4 AEs with exception of neutropenia (8% vs. 2%, respectively; p=0.015). There was no difference in QoL parameters between intervention and placebo arms that were identified during the induction or maintenance portions of therapy. The PARAMOUNT authors presented an update on secondary trial outcomes including OS at the 2012 ASCO annual meeting.[27] Pemetrexed continuation resulted in a 22% reduction in death, with a median OS from the time of randomization of 13.9 months vs. 11.0 months in placebo plus BSC (HR=0.78; 95% CI 0.64-0.96; p=0.0195), with an OS difference that persisted when evaluated from time of induction doublet therapy (16.9 months vs. 14 months; HR=0.78; 95% CI 0.64-0.96; p=0.0191). The percentage of pemetrexed maintenance patients alive at 12 and 24 months was 58% and 32%, compared to 45% and 21% in the placebo plus BSC cohort. A majority of patients on continuation maintenance pemetrexed were able to proceed with second line therapy, with 64% of patients receiving post-discontinuation therapy in the pemetrexed continuation arm versus 72% of patients in the BSC arm. Continuation of pemetrexed likely confers a clinical benefit in NSCLC partly because it is very well tolerated with minimal grade 3/4 AEs, even during long-term use.

Continuation Maintenance: Targeted Therapies

Bevacizumab, a humanized monoclonal antibody against the VEGFA ligand, has been evaluated in multiple trials and is a common continuation maintenance agent used in practice today. The initial phase III trial, Eastern Cooperative Oncology Group (ECOG) 4599, was conducted by Sandler et al. who randomized 878 NSCLC patients to paclitaxel plus carboplatin every 3 weeks for 6 cycles with or with bevacizumab at 15mg/kg dose with a primary endpoint of OS.[12] It is worth noting that patients with squamous cell histology, a history of therapeutic anticoagulation, hemoptysis, or brain metastasis were excluded based upon the occurrence of fatal hemorrhagic events during a prior phase II study of bevacizumab in this population.[28] Patients that responded to or had stable disease on doublet therapy plus bevacizumab continued bevacizumab as a single agent. Patients randomized to the bevacizumab arm had a higher median OS (12.3 vs. 10.3 months; HR=0.79; 95% CI 0.67-0.92; p=0.003), with a higher ORR (35% vs. 15%; p<0.001) and median PFS (6.2 vs. 4.5 months; HR=0.66; 95% CI 0.57-0.77; p<0.001). Toxicities included increased grade 3/4 hypertension in the bevacizumab arm (7.0% vs. 0.7%; p<0.001) as well as clinically significant bleeding (4.4% vs. 0.7%; p<0.001). There were 15 treatment related deaths in the bevacizumab arm vs. 2 in the standard of care arm, which included 5 deaths due to hemoptysis and 2 due to hematemesis. The rate of at least one grade 3 or worse event were statistically higher in the cohort of patients 70 and older (87% vs. 61%; p<0.001). [29] Additional retrospective analysis revealed that patients that developed hypertension had a lower HR for death and improved PFS.[30] Yet another retrospective analysis of phase II/III data revealed that tumor cavitation at baseline was predictive for the pulmonary hemorrhage recorded in both trials. [31]

The AVAIL (Avastin in lung cancer) trial performed by Reck et al. randomized 1,043 NSCLC patients with nonsquamous histology to placebo, bevacizumab 7.5mg/kg, and bevacizumab 15mg/kg combined with cisplatin and gemcitabine (1250mg/m^2) for up to 6 cycles.[32] Patients with stable or responsive disease on either bevacizumab arm could continue bevacizumab every 3 weeks until disease progression or toxicity. The primary endpoint was amended from OS to PFS, and the trial was not powered to detect a difference between the two bevacizumab doses. Median PFS was significantly higher for both treatment arms: 6.1 months vs. 6.7 months (p=0.003) vs. 6.5 months (p=0.03) in the placebo, low dose bevacizumab and high dose bevacizumab arms, respectively, with similar AE rates among all treatment arms including hemorrhage (<1.5%) despite inclusion of a small group of patients on therapeutic anticoagulation (9%).

Recently, the PointBreak investigators have published results of their phase III trial using a maintenance approach with pemetrexed and the anti-VEGF ligand monoclonal antibody bevacizumab. This trial was proposed after phase II data where 50 patients with nonsquamous histology were enrolled in an single arm open label trial to receive carboplatin, pemetrexed, and bevacizumab at a 15mg/kg dose every 3 weeks for 6 cycles followed by continuation of both pemetrexed and bevacizumab in patients with stable or responding disease until dose limiting toxicity or progression.[33] ORR was 55%, with PFS of 7.8 months and OS of 14.1. In the phase III setting, nonsquamous patients were randomized to pemetrexed, carboplatin, plus bevacizumab (arm 1, n=472) with combined

continuation maintenance therapy with pemetrexed and bevacizumab for patients without disease progression (n=292) vs. paclitaxel, carboplatin plus bevacizumab (arm 2, n=467) with continuation maintenance bevacizumab for patients without disease progression (n=298).[34] PFS from the time of randomization was 6 vs. 5.6 months in arm 1 vs. arm 2 (HR=0.83; 95% CI 0.71-0.96; p=0.012) with an OS difference of 13.4 vs. 12.6 months that was not statistically significant (HR=1.0; 95% CI 0.86-1.16; p=0.949). In a preplanned analysis addressing the maintenance components of the trial, the PFS was 8.6 months in arm 1 and 6.9 months in arm 2, with OS of 17.7 vs. 15.7 months, respectively (p values not provided). There was higher grade 3/4 hematologic AEs in arm 1 with anemia (14.5% vs. 2.7%; p<0.05), thrombocytopenia (23.3% vs. 5.6%; p<0.05) higher in the pemetrexed arm while grade 3/4 neutropenia occurred at a significantly higher rate in arm 2 (25.8% vs. 40.6%; p<0.05). It is worth noting that these phase III trials were not specifically designed to evaluate bevacizumab's utility as a maintenance agent *per se*, and the drug's impact on PFS, OS, and QoL past induction with platinum doublet therapy remains an unanswered question.

Cetuximab, a chimeric monoclonal antibody against the extracellular portion of the epidermal growth factor receptor (EGFR) has been evaluated in conjunction with first line doublet therapy in 2 phase III randomized trials. In the FLEX (First-Line ErbituX in lung cancer) trial, Pirker et al. randomized NSCLC patients with EGFR as determined by IHC to in an open label fashion to cisplatin and vinorelbine every 3 weeks with or without weekly cetuximab (400mg/m^2 IV loading dose for week 1 followed by 250mg/m^2 thereafter) for up to 6 cycles with continuation of cetuximab past induction until progression or toxicity with OS as the primary endpoint. [13] There was a significant improvement in OS in the cetuximab group (11.3 months vs. 10.1 months; HR=0.871; 95% CI 0.762-0.996; p=0.044) with 10% of patients in the cetuximab arm developing grade 3 or higher acneiform rash. Retrospective analysis revealed that median OS was higher in the cetuximab arm than in the control group (12.0 vs. 9.6 months; HR=0.73, p=0·011).[35] Additional retrospective analyses of biomarkers of interest (*KRAS* and *EGFR* mutation status, *EGFR* copy number, PTEN expression) were not predictive for efficacy in the cetuximab arm.[36]

Another phase III trial conducted by Lynch, et al. randomized 676 NSCLC patients without using EGFR status for eligibility to carboplatin plus taxane (TC) chemotherapy (either docetaxel at 75mg m^2 or paclitaxel 225mg/m^2) every 3 weeks for up to 6 cycles with weekly cetuximab (400mg/m^2 IV week 1, then 250mg/m^2 weekly) administered until progression/ toxicity vs. TC alone.[37] The primary endpoint was PFS, with OS, ORR, and QoL as secondary endpoints. Median PFS was nonsignficant (4.4 months with cetuximab vs. 4.24 months with TC; HR=0.902; 95% CI 0.761-1.069; p=0.236) as was median OS (9.69 months cetuximab arm vs. 8.38 months with TC; HR=0.890; 95% CI 0.754-1.051; p=0.169). ORR was statistically significant, with the cetuximab arm at 25.7% vs. 17.2 % for TC alone (p=0.007) with a similar AE profile as seen in the FLEX trial. An open-label phase III trial (SWOG 0819, NCT00946712, Table III) is currently enrolling, utilizing carboplatin and paclitaxel (with the addition of bevacizumab per treating physician discretion) with randomization (1:1) to weekly cetuximab versus observation. EGFR expression by IHC is being collected on all patients upon enrollment for further biomarker analysis based in part upon the encouraging OS results for patients with high EGFR IHC expression in the FLEX

trial.[35] It is important to note that none of the aforementioned trials were designed to directly address whether the maintenance portion cetuximab therapy impacts PFS and OS. To date this agent is not approved for use in stage IIIB/IV NSCLC by the FDA or EMA. Additional prospective trials such as SWOG 0819 are needed with improved biomarker selection in order to determine if addition of cetuximab induction *and* maintenance lead to clinically meaningful outcomes for NSCLC patients.

EGFR TKIs have also been investigated in 4 phase III trials in conjunction with conventional chemotherapy, two that used gefitinib[38, 39] and two that used erlotinib.[40, 41] Both the INTACT (Iressa NSCLC Trial Assessing Combination Treatment) trials[38, 39] randomized NSCLC patients irrespective of *EGFR* mutation status to platinum-based doublet chemotherapy (cisplatin plus gemcitabine and carboplatin plus paclitaxel) plus either gefitinib at 500mg/day, gefitinib 250mg/day or placebo. Both trials continued gefitinib until progression or unacceptable toxicity. Both trials failed to meet their primary endpoint of median OS (INTACT 1: 9.9 months, 9.9 months, 10.9 months and INTACT 2: 8.7, 9.8, and 9.9 months for gefitinib 500mg/day, 250/mg, day, and placebo, respectively). The TRIBUTE (Tarceva responses in conjunction with paclitaxel and carboplatin) trial was the first phase III study to employ erlotinib in combination with first line chemotherapy, randomizing NSCLC patients regardless of *EGFR* mutation status to 6 cycles of carboplatin/paclitaxel with either erlotinib at 150mg/day or placebo followed by continuation of TKI until progression or unacceptable toxicity.[41] The trial failed to meet its primary endpoint of median OS, with final results nearly identical in the erlotinib (10.6 months) and placebo (10.5 months; p=0.95) arms. Gatzemeier, et al. conducted the TALENT (Tarceva Lung Cancer Investigation) trial with comparator arms of gemcitabine plus cisplatin were combined with erlotinib at 150mg/day for 6 cycles with continuation of erlotinib until toxicity or disease progression.[40] The primary endpoint of median OS was not met (43 weeks in erlotinib arm vs. 44.1 in placebo; HR=1.06; 95% CI 0.90-1.23; p=0.49) with no significant difference in secondary endpoints of TTP, ORR, or QoL. All of the aforementioned trials did not enroll patients by *EGFR* mutation status, nor were they specifically designed to address use of EGFR TKI's as continuation maintenance therapy. A full list of continuation maintenance trails which continue the non-platinum portion of the induction therapy is listed in Table I.

Switch Maintenance Therapy

Switch Maintenance: Conventional Chemotherapy

Switch maintenance therapy has been addressed recently in a 2011 ASCO focused practice guideline update, where it is defined as an “alternative therapy administered to patients who have undergone first-line therapy for a specified number of cycles.”[7] Unlike second line therapy, switch therapeutic agents are administered immediately after first line chemotherapy in the absence of radiographic progression or demonstrated resistance to first line therapy. Phase III trials investigating switch maintenance have administered maintenance agents with non-overlapping mechanisms of action compared to the original drugs used as first line therapy under the principle that patients will not be cross-resistant and that they may avoid cumulative toxicity.

Phase III data for switch maintenance therapy was first reported by Westeel, et al. who randomized 573 stage IIIB/IV patients to two monthly cycles of mitomycin, ifosfamide and cisplatin (MIC) with subsequent thoracic radiotherapy for the IIIB cohort or four additional monthly cycles for stage IIIB (with malignant effusions) and stage IV NSCLC patients.[42] 181 patients with responding or stable disease were then randomized to receive maintenance vinorelbine for 6 months or BSC with a primary endpoint of OS. Only 23% of patients were able to complete the planned 6 months of vinorelbine, with discontinuation due to progressive disease (38%) and toxicity (21%) being most common. The trial failed to meet its primary endpoint of median OS with identical 12.3 months OS (p=0.65) in both vinorelbine and BSC groups, nor did it meet a secondary endpoint of improved PFS, with median PFS of 5 months on vinorelbine vs. 3 months in BSC (p=0.11).

Fidias et al. conducted the first phase III trial employing switch maintenance using a modern platinum-based doublet chemotherapy, randomizing 309 patients with IIIB/IV NSCLC who had yet to progress on 4 cycles of gemcitabine (1,000mg/m^2 IV cycle days 1 and 8) and carboplatin (AUC 5 every 21 days) to immediate docetaxel (75mg/m^2 IV every 21 days) for a maximum of 6 cycles vs. planned second line (delayed) docetaxel at demonstration of progression.[43] The study was powered to detect a difference in its primary endpoint of OS, with PFS and QoL as pertinent secondary endpoints. There was a numerical difference in median OS between the two groups that did not meet statistical significance, with OS of 12.3 months for the immediate docetaxel group vs. 9.7 months for the delayed docetaxel arm (p=0.853). Median PFS was statistically significant between the two cohorts (5.7 months for immediate docetaxel vs. 2.7 months for delayed docetaxel; p=0.0001) and there was no significant difference in toxicity profiles or QoL assessment between the two groups. Of note, only 63% of randomized patients received second line docetaxel in the delayed docetaxel arm, with the most common reasons for not receiving planned treatment being decline in performance status and clinical deterioration. Additional post-hoc analysis demonstrated identical OS of 12.5 months in each cohort for those patients that received docetaxel chemotherapy, suggesting that the observed benefit of switch maintenance docetaxel was due to a higher likelihood of receiving second line docetaxel prior to decline in performance status or death. It is also worth noting that this remains the only trial that directly addresses the timing of second line agents as either switch maintenance or early second line therapies.

Recently, clinical trials addressing switch maintenance using third generation cytotoxics have been reported. Cilueanu et al. published the first phase III trial using pemetrexed as a switch maintenance agent, randomizing stage IIIB/IV NSCLC patients irrespective of histology after completion of 4 cycles of platinum-based doublet of choice (either cisplatin or carboplatin paired with gemcitabine, paclitaxel or docetaxel) with objective response or stable disease to pemetrexed at 500mg/m^2 every 3 weeks until unacceptable toxicity or disease progression versus BSC with vitamin B12, folic acid, and dexamethasone administered to both arms.[44] The trial was powered for and met its primary endpoint of PFS, with median PFS in the pemetrexed cohort of 4.3 months vs. 2.6 months for BSC (HR=0.50; 95% CI 0.42-0.61; p<0.0001). Median OS as a secondary endpoint was also significant, with 13.4 months in the pemetrexed cohort vs. 10.6 months in the BSC arm (HR=0.79; 95% CI 0.65-0.95; p=0.012). Toxicity was higher in the treatment group but was

reported as manageable with 16% grade 3/4 events in pemetrexed vs. 4% in BSC, the most common being fatigue (5% vs. 1%) and neutropenia (3% vs. 0%). The benefit of pemetrexed switch maintenance was restricted to the patients with nonsquamous histology with a median PFS in this cohort of 4.4 months vs. 1.8 in the nonsquamous BSC patients (HR=0.44; 95% CI 0.36-0.55; p<0.0001) and a median OS difference of 15.5 months vs. 10.3 months (HR=0.70; 95% CI 0.56-0.88; p=0.002). In comparison, the squamous cell histology cohorts had a 2.8 month median PFS in their treatment arm, which was similar to the median PFS of 2.6 months for squamous cell NSCLC patients randomized to BSC (HR=0.69; 95% CI 0.49-0.98; p=0.039) and a numerically inferior OS compared to BSC (9.9 vs. 10.8 months; HR=1.07; 95% CI 0.77-1.50; p=0.678). Of note, 51% of patients in the pemetrexed cohort received further treatment after progression vs. 67% of the BSC arm, with only 19% of patients in the BSC arm receiving pemetrexed upon disease progression as second line therapy. Given that only a minority of patients in the control arm received pemetrexed at the time of disease progression, this trial did not allow for comparisons between immediate administration of pemetrexed as switch maintenance and pemetrexed as second line therapy at the time of progression. Still, PFS, OS and other secondary outcomes from this trial compare favorably to previously reported phase III trials investing pemetrexed as a second line agent.[45] Both the EMA and the FDA have approved pemetrexed as switch maintenance therapy for NSCLC patients with nonsquamous histology whose advanced or metastatic disease has not progressed four cycles of first line platinum based chemotherapy.

Switch Maintenance: Targeted Agents

As agents that target specific molecular drivers of NSCLC, TKIs and monoclonal antibodies have an innate appeal for switch maintenance therapy. These agents often show little overlapping toxicities with conventional cytotoxic chemotherapy and their use in switch maintenance has been investigated in several randomized controlled trials. Cappuzzo et al. conducted the SATURN (Sequential Tarceva in Unresectable NSCLC) trial, which evaluated the efficacy of erlotinib as a switch maintenance agent in NSCLC patients, enrolling 1949 NSCLC patients to receive 4 cycles of platinum based chemotherapy as first line therapy.[46] Patients with stable or responding disease (n=889) following completion of first line therapy were randomized to erlotinib or placebo until progression or unacceptable toxicity. In addition to age, performance status, chemotherapy regimen, smoking history, and region, patents were stratified by EGFR IHC expression in order to address co-primary endpoints of PFS in the entire cohort and PFS in patients with high expression of EGFR by IHC. There was a modest improvement in median PFS in the erlotinib arm of 12.3 vs. 11.1 weeks in the placebo group (HR=0.71; 95% CI 0.62-0.82; p< 0.0001) and an identical PFS of 12.3 vs. 11.1 weeks (HR=0.69; 95% CI 0.58-0.82; p<0.0001) in patients with high expression of EGFR by IHC. Patients with an *EGFR* activating mutation demonstrated a much larger benefit (median PFS 44.6 weeks on erlotinib vs. 13.0 weeks for placebo; HR 0.10; 0.04-0.25; p<0·0001) as expected from other studies using EGFR TKI's in *EGFR*-mutated NSCLC.[8, 9, 47, 48] The trial also demonstrated a modest but statistically significant median OS benefit of 12 vs. 11 months in the non-selected erlotinib group compared to placebo (HR=0.81; 95% CI 0.70-0.95; p=0.009). Median OS for the patient cohort with *EGFR* activating mutations had not yet been reached at the time of study publication

(HR=0.83; p=0.68). Preplanned subgroup analysis demonstrated no difference in PFS and OS regardless of ethnicity, gender, tobacco use, or performance status. There was no mandated use of EGFR TKI as second line therapy and as such there was a relatively low rate of subsequent EGFR TKI use in the placebo group (16%). Toxicity was higher in the erlotinib arm with rash and diarrhea of any grade of 60% and 20% in the erlotinib arm vs. 9% and 5% for placebo. Grade 3/4 toxicity in the erlotinib versus placebo arm included rash (9% vs. 0%) diarrhea (2% vs. 0%), with serious adverse event rate of 11% in erlotinib arm vs. 8% in placebo, the most common being pneumonia (2% vs. <1%). Lastly, there was no significant difference for time to deterioration of QoL in between the two study arms. Given the statistically significant but modest clinical benefit in PFS and OS in this unselected study cohort, erlotinib was approved by the FDA and the EMA for use in maintenance therapy for advanced NSCLC patients after stable or responsive disease with first line platinum therapy. As expected, the PFS differences in the *EGFR* mutant cohort were dramatic, however the 1.2 week PFS difference in the nonselected cohort is of debatable clinical significance, and an informed discussion with *EGFR* wild type patients regarding the absolute benefit and expected toxicity should occur prior to employing this maintenance strategy compared to switch maintenance or continuation maintenance with pemetrexed.[27, 44]

As discussed in ‘Continuation Maintenance: Conventional Chemotherapy’, Perol et al. randomized advanced NSCLC patients with stable or responsive disease after 4 cycles of cisplatin and gemcitabine to daily maintenance erlotinib (150mg/day) vs. gemcitabine vs. BSC.[49] When possible, *EGFR* mutational analysis (n=14) and EGFR expression via IHC (n=261) was collected on tumor biopsy samples at enrollment. Median PFS was 2.9 months (erlotinib) vs. 1.9 months for BSC and favored the erlotinib arm (HR=0.69; 95% CI 0.54-0.88; p=0.003). However, this PFS benefit did not translate to a statistically significant median OS survival benefit (11.4 vs. 10.8 months in erlotinib vs. BSC, respectively; HR=0.87; 95% CI, 0.68-1.13; p=0.3043). EGFR IHC status had no statistically significant benefit for either EGFR positive (HR=0.76; 95% CI 0.49-1.18) or EGFR IHC–negative tumors (HR=0.77; 95% CI 0.47-1.28). Survival analysis was not performed by the study on the *EGFR* mutation positive cohort due to the small sample size.

The role for the EGFR TKI gefitinib has been investigated in 3 switch maintenance phase III trials with variable degrees of clinical impact. Takeda et al. reported the final results of their West Japan Thoracic Oncology Group trial (WJTOG0203) where 604 advanced NSCLC patients were randomized after 3 cycles of a platinum doublet to gefitinib (250mg/day) or up to 3 additional cycles of chemotherapy.[50] While there was a statistically significant difference in median PFS in the gefitinib arm (4.6 vs. 4.3 months, HR=0.68; 95% CI, 0.57-0.80; p< 0.001), this trial failed to meet is primary endpoint of OS (13.7 vs. 12.9 months; p=0.11). Patients with *EGFR* activating mutations were not assessed in this trial as these mutations had yet to be established as a predictive biomarker for EGFR TKI's at the time of accrual.

Zhang et al. conducted the INFORM (Iressa in NSCLC FOR Maintenance) multicenter phase III trial where 296 patients across China with advanced NSCLC who had not progressed after 4 cycles of first line platinum-based doublet chemotherapy. Patients were randomized to gefitinib (250mg/day) or placebo until disease progression or unacceptable

toxicity.[51] While patients with a known *EGFR* mutation were excluded from the trial to avoid selection bias, *EGFR* mutation analysis was performed in 39 patients in the experimental arm and 40 patients in the placebo arm. The primary endpoint, PFS, was achieved with a median PFS of 4.8 months for gefitinib vs. 2.6 months with placebo (HR=0.42; 95% CI 0.33-0.55; p< 0.0001) with a greater benefit for the patients harboring an *EGFR* activating mutation (16.6 months vs. 2.8 months; HR=0.17; 95% CI 0.07-0.42). Further subgroup analysis revealed that the benefit was restricted to the *EGFR* mutation positive cohort, as *EGFR* wild type patients had no difference in PFS (2.7 vs. 1.5 months; HR=0.86, 95% CI 0.48-1.51; p=0.0063). There was no statistically significant benefit in median OS amongst the entire treatment group (18.7 vs. 16.9 months; HR=0.84; 95% CI 0.62-1.14; p=0.26), in part due to inadequate power for this secondary endpoint, and also due to higher proportion of patients in the placebo arm receiving second line therapy compared to the gefitinib cohort (62% in placebo group, 29% of which received subsequent gefitinib vs. 43% for gefitinib arm). Median OS data for the *EGFR* mutation subgroup was not provided.

Lastly, Gaafar et al. conducted EORTC 08021/ILCP 01/03 trial where advanced NSCLC patients with nonprogressive disease after 4 cycles of platinum-based chemotherapy were randomized to gefitinib (250mg/day) vs. placebo.[52] While the study planned to randomize 598 patients, only 173 patients were randomized and the study was closed prematurely. As such, the study's primary endpoint, OS, was underpowered and not statistically different between study groups (10.9 vs. 9.4 months, gefitinib and placebo, respectively; p=0.204) with statistically significant improvement in PFS in the gefitinib cohort of 4.1 vs. 2.9 months, respectively (HR=0.61; 95% CI 0.45-0.83; p=0.0015). Currently, data from these gefitinib switch maintenance trials do not provide adequate evidence to support its use in the maintenance setting, and gefitinib has yet to gain approval from major regulatory agencies for maintenance use.

Bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF) was evaluated by Miller, et al. via the ATLAS (Avastin and Tarceva in Lung Cancer Study), which was designed to study the efficacy of two different regimens, erlotinib plus bevacizumab versus bevacizumab alone in a switch maintenance setting.[53] This trial enrolled 1,160 patients with advanced non-squamous, NSCLC (including patients that were anticoagulated with low molecular weight heparin and those with treated brain metastasis) and administered 4 cycles of bevacizumab at 15 mg/kg every 3 weeks with a first line platinum-based chemotherapy selected by the provider. Of these, 768 patients who had stable or responding disease after 4 cycles were randomized to continuation bevacizumab (B) or bevacizumab plus 150mg/day of erlotinib (B+E). The primary objective was detection of a PFS difference in the B+E cohort over the B treatment group, with secondary outcomes of OS and safety assessments. The trial met its primary endpoint with a modest improvement in PFS of 4.8 months in the B+E cohort vs. 3.7 months in the B cohort (HR=0.72; 95% CI 0.59-0.88; p=0.0012). However, this did not translate into a difference in median OS (15.9 vs. 13.9 months for B+E and B, respectively; HR=0.91; 95% CI 0.80-1.04; p=0.27) with greater toxicity in the B+E arm. Higher rates of rash (10.4% vs. 0.5%) and diarrhea (9.3% vs. 0.8%) were observed in the B+E arm vs. the B arm, respectively. The

number of patients who received addition post-study therapy was similar in each arm (55% in B+E vs. 50% in B). This trial does not address the question of whether continuing bevacizumab past first line therapy confers additional benefit, and its findings imply that the addition of an additional targeted agent in the maintenance setting provided marginal benefit in PFS and no demonstrable OS benefit. However, an atypically high median OS time in the control cohort coupled with the fact that the trial was stopped after the first interim analysis when it met its primary endpoint limits the ability to detect a difference in OS. A summary of switch maintenance trials is supplied in Table II.

Meta-Analyses of Maintenance Trials

With exception of a few selected trials [27, 44, 46] most clinical trials that specifically address maintenance therapy in NSCLC demonstrate variable improvements in PFS over their control arms without a statistically significant improvement in OS. However, many of these trials were either not powered to detect a difference in OS, could not control for subsequent salvage therapies post study, or both. Recently, several meta-analyses have attempted to broadly assess the impact of maintenance chemotherapy with second and third line chemotherapy agents with a primary endpoint of OS. Lima et al. indirectly addressed the concept of continuation maintenance via a meta-analysis of 1559 patients from 7 clinical trials in order to determine PFS and OS differences between trial with low (≤4 cycles) and high (≥4 cycles) number of fixed cycles vs. continuation of treatment until disease progression or unacceptable toxicity.[54] The study was designed to investigate modern platinum-based doublet chemotherapy regimens, with one notable exception,[55] and excluded trials employing targeted agents. Treatment for longer than 4 cycles was not associated with a statistically significant difference in median OS (HR=0.97; 95% CI 0.84-1.11; p=0.65). Indeed, in trials using a third generation agent there was a trend towards increased mortality for more than 4 cycles of chemotherapy (HR=1.08; 95% CI 0.90-1.28; p=0.28). Patients treated with more than 4 cycles of chemotherapy did have a significant improvement in median PFS (HR=0.75; 95% CI 0.60-0.85; p<0.0001) but this was associated with greater degree of hematological toxicity (odds ratio=1.31; 95% CI 1.01-1.69; p=0.04).

Maintenance was also addressed in a meta-analysis by Soon et al. where 13 randomized controlled trials with 3,027 patients that compared a fixed number of treatment cycles to continuation of therapy until progression/unacceptable toxicity were assessed.[56] While extension of chemotherapy did improve PFS (HR=0.75; 95% CI 0.69-0.81; p< 0.00001) there was only a modest improvement in median OS (HR= 0.92; 95% CI 0.86-0.99; p=0.03). There was a greater impact on PFS in trials using third generation chemotherapy regimens compared to older regimens (HR 0.7 vs. 0.92; p=0.003) and the modest OS benefit observed only became statistically significant when the trial of switch maintenance pemetrexed was included.[44] Treatment related adverse events were more pronounced in all trials using continuation therapy, and QoL endpoint results were variable, with 2 of the 7 trials including QoL assessments reporting a net negative effect on QoL, with no detectable difference in QoL in the remaining trials.

Behera et al. reported results of a meta-analysis evaluating 10 trials with 3451 patients with single agent continuation or switch maintenance after a fixed number of chemotherapy cycles.[57] In aggregate, the median OS (HR=0.87; 95% CI 0.80-0.88; p<0.0001) and PFS (HR=0.84; 95% CI 0.80-0.88; p< 0.0001) were improved with maintenance therapy. Subgroup analysis revealed a greater benefit with switch maintenance in both median PFS (HR=0.71; 95% CI 0.66-0.77; p<0.0001) and OS (HR=0.86; 95% CI 0.8-0.93; p=0.0005) but only a modest improvement for continuation maintenance in PFS (HR=0.92; 95% CI 0.87-0.98; p=0.007) and no improvement in OS (HR=0.92; 95% CI 0.77-1.08; p=0.33).

Zhang, et al. evaluated 8 trials with a total of 3,736 patients using either a switch maintenance strategy or a continuation maintenance strategy.[58] There was an improvement in median OS when switch maintenance was compared to placebo/observation (HR=0.85; 95% CI 0.79-0.92; p<0.001) with a more substantial improvement in PFS (HR=0.67; 95% CI 0.57-0.78; p<0.001). Continuation maintenance assessments revealed a trend towards improvement in OS that was not statistically significant (HR=0.88; 95% CI 0.74-1.04) despite a marked improvement in PFS (HR=0.53; 95% CI 0.43-0.65; p<0.001).

While all aforementioned trials have included third generation chemotherapy, only two of the meta-analysis included and evaluated the use of targeted therapies and EGFR TKI's as a specific subgroup. Behera et al. reported a statically significant improvement in median OS (HR=0.86; 95% CI 0.78-0.95; p=0.006) and PFS (HR=0.76; 95% CI 0.70-0.83; p< 0.0001) in this cohort,[57] with Zhang et al. reporting a more modest but statistically significant improvement in median OS for maintenance strategies versus placebo or observation (HR=0.87; 95% CI 0.80-0.95; p=0.001) and PFS (HR=0.74; 95% CI 0.66-0.83; p< 0.001). Trials employing bevacizumab as a maintenance agent were included the Behera and Zhang meta-analyses. It is notable that the recently released OS data from the PARAMOUNT trial were not available for inclusion in these meta-analyses, and these results could have had an effect on the above studies' OS results if available.[27]

Maintenance Therapy: Future Directions

There are several multi-institution clinical trials currently open specifically addressing ongoing concerns with NSCLC maintenance therapy (Table III). Briefly, many of these trials are attempting to address open questions regarding the use of targeted therapy with trial designs specifically addressing the role of bevacizumab as a maintenance agent, the role of cetuximab as a first line and maintenance agent for NSCLC, and the use of third generation and/or targeted agents with non-overlapping toxicities as dual maintenance therapy. Sunitinib, an oral multi-targeted TKI with antiangiogenic activity, is being investigated in CALGB 30607, a phase III trial that randomizes patients with non-progressive disease after 4 cycles of carboplatin plus paclitaxel to either oral sunitinib or placebo until progressive disease or unacceptable toxicity (NCT00693992). Previous open label phase II experience with 66 patients demonstrated potential value with this approach with an ORR of 27%, although the study failed to meet is primary endpoint of overall survival at 1 year of ≥ 55% (40.5% in the study population). [59]

In addition, several immune and vaccine based therapy strategies are being evaluated in NSCLC, with several phase III trials currently enrolling patients (Table III). This treatment approach challenges the current perception of maintenance chemotherapy, as they attempt to harness active immunity to induce a tumor specific immune response. The concept of vaccine based therapy as it applies to both early stage and advanced NSCLC has been recently addressed in another comprehensive review. [60] Passive immune therapies in the form of adoptive T-cell immunotherapy are also under investigation in trial designs including continuation of immunotherapy after completion of a fixed cycle number of first line carboplatin and paclitaxel. A phase III trial of ipilimumab is currently enrolling patients (NCT1285609) based upon results of a recently published phase II trial where 204 untreated NSCLC patients were randomized (1:1:1) to receive 6 cycles of carboplatin and paclitaxel plus placebo, concurrent ipilimumab (4 concurrent 10 mg/kg doses with chemotherapy followed by 2 doses of placebo injection) or phased ipilimumab (two doses of concurrent placebo followed by four doses of 10mg/kg with each subsequent cycle) with continuation maintenance ipilimumab therapy offered to both concurrent and phased ipilimumab arms.[61] Phased ipilimumab, concurrent ipilimumab and control arms demonstrated an immune related PFS (irPFS) of 5.7, 5.5, and 4.7 months. While the differences between phased ipilimumab and control was statistically significant (HR=0.69; p=0.02), the irPFS differences did not reach statistical significance in the concurrent ipilimumab group (HR=0.88; p=0.25). There was a nonsignficant trend toward an improvement in median OS in the phased ipilimumab group compared to placebo (12.2 vs. 8.3 months; HR=0.87; p=0.23) while the median OS in the concurrent ipilimumab arm was similar to that of the control group (9.7 vs. 8.3 months; HR=0.99; p=0.48) There was an increase in immune related AEs in the phased (15%) and concurrent (20%) ipilimumab groups over control (6%). Based on statistically significant increase in irPFS and a trend towards OS in the phased ipilimumab arm the double blind, placebo controlled phase III trial is currently enrolling using the same carboplatin and paclitaxel backbone with phased Ipilimumab administered to the experimental arm.

Several phase III maintenance vaccine trials are accruing or have recently completed enrollment for advanced NSCLC using different vaccine strategies to deliver tumor antigen. Belagenpumatucel-L, an allogeneic vaccine consisting of 4 different NSCLC cell lines of different histology has recently completed phase III enrollment (NCT00676507). In a phase II dose-range trial (12.5, 25, or 50 × 10^6 cells/injection), patients with advanced NSCLC who received a high dose of the vaccine (> 25× 10^6 cells/injection) demonstrated a 2 year survival of 47% vs. 18% in low dose groups when the vaccine was administered monthly after first line chemotherapy.[62] TG4010, an attenuated live-virus vaccine, is engineered for high expression of MUC1 and IL-2 and is currently enrolling to a phase III trial (NCT01383148). In an open-label, randomized phase II trial, 148 patients with MUC1 tumor expression receiving subcutaneous TG4010 (weekly × 6 weeks then q3 weeks until disease progression) after first line cisplatin/gemcitabine had a 6 month PFS of 44% vs. 35% (p=0.13) and a higher ORR (44% vs. 27%; p=0.03) compared to control patients receiving first line cisplatin/gemcitabine alone.[63] A recombinant human vaccine coupling human EGF to a carrier protein was evaluated in a phase II study.[64] Patients with advanced NSCLC (n=80) were randomized to cyclophosphamide priming (200mg/m^2) followed by

vaccine (50 μg equivalents of EGF days 1, 7, 14, 28 days followed by monthly injections until progression) versus BSC. There was a non-significant trend towards OS in the vaccinated group (6.5 vs. 5.3 months; p=0.098) with patients <60 years of age demonstrating a larger and significant OS improvement (11.6 vs. 5.3 months; p=0.124). This vaccine is currently being investigated in a phase II/III trial (NCT00516685). Given recent advances in early phase trials with other active immunotherapy agents demonstrating clinical response, this area will certainly be an active area of research for maintenance therapy in NSCLC. [65, 66]

Lastly, correct patient selection for maintenance therapy remains an active area of investigation, specifically with regards to clinicopathologic and biologic heterogeneity of NSCLC. Pemetrexed, the only conventional chemotherapy agent with current FDA and EMA approval for maintenance therapy, has demonstrated differential efficacy in advanced nonsquamous histology.[25] Bevacizumab has been approved by the FDA for first line use in advanced nonsquamous NSCLC only given safety concerns in the squamous cohort during phase II trials leaving no current maintenance chemotherapy options for patient with squamous cell carcinoma that have demonstrated improvement in OS and are approved for use by major regulatory agencies.[28] Given that several ongoing phase III trials (Table III) exclude patients with squamous cell histology, a safe and effective maintenance therapy for this subgroup is an area of active need. While erlotinib is approved in the United States and Europe irrespective of histology for switch maintenance, the clinical benefit of this agent in squamous histology is questionable, with the SATURN study demonstrating an nonsignificant trend towards improvement in PFS in 360 patients with squamous histology (HR=0.76; 95% CI 0.60-0.95; p>0.05) and OS (HR=0.86; 95% CI 0.68-1.10; p>0.05).[46]

Maintenance Therapy: Summary and Recommendations

Given current data available, the authors agree with current ASCO guidelines regarding first line therapy of NSCLC, and recent 2011 updates addressing maintenance in particular.[7] Briefly, NSCLC patients whose disease is stable but not responding to first line cytotoxic chemotherapy should have platinum chemotherapy discontinued after 4 cycles of treatment. Patients with responding disease tolerating initial combination cytotoxic chemotherapy may proceed with 6 total cycles of platinum-based chemotherapy. Patients with ECOG PS ≤ 2 with stable or responsive disease after 4-6 cycles of chemotherapy should be considered for maintenance chemotherapy. For NSCLC patients with nonsquamous histology initially treated with pemetrexed as part of a platinum doublet, we believe that continuation of pemetrexed as a maintenance agent until progression or unacceptable toxicity is warranted given recent updated data from the PARAMOUNT trial demonstrating statistically significant difference in OS using this strategy. For patients with squamous histology or nonsquamous patients with non-pemetrexed containing first line therapy, switch maintenance therapy with erlotinib or pemetrexed (in nonsquamous cohorts) may be considered. These patients must be selected carefully with an informed discussion regarding the use of immediate switch maintenance vs. early treatment at the time of progression. NSCLC patients found to harbor an *EGFR* activating mutation following initiation of first line chemotherapy should consider switch maintenance erlotinib following a fixed number of cycles of chemotherapy with the caveat that that patients with *EGFR* mutations treated

with pemetrexed-based chemotherapy may also benefit from continuation of single agent pemetrexed until disease progression or intolerance before switch to erlotinib. Patients with nonsquamous histology placed on bevacizumab as part of their first line therapy should consider continuation of this therapy up to a year after 4-6 cycles of their cytotoxic therapy if this agent is well tolerated, with the caveat that it is unknown if bevacizumab's benefit occurs during induction chemotherapy alone, during the maintenance phase, or both. In general, the recent availability of new chemotherapy (pemetrexed), TKI's, and immunotherapy agents with a more tolerable or nonoverlapping toxicity profile have enabled maintenance strategies to be successful, and the approach should be considered in patients responding to first line therapy when possible.

Acknowledgments

Doebele, RC: Research grants from Eli-Lilly & Co. and ImClone Systems.

Funding Sources: No outside funding sources used for the preparation of this manuscript

References

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin. 2010 Sep-Oct;60(5): 277–300. [PubMed: 20610543]
2. Howlader, N.; Noone, A.; Krapcho, M.; Neyman, N.; Aminou, R.; Altekruse, S., et al. Bethesda, MD: National Cancer Institure; 2012. SEER Cancer Statistics Review, 1975-2009 (Vintage 2009 Populations). Available from: http://seer.cancer.gov/csr/1975_2009_pops09/
3. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011 Mar-Apr;61(2):69–90. [PubMed: 21296855]
4. Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med. 2002 Jan 10; 346(2):92–8. [PubMed: 11784875]
5. Azzoli CG, Baker S Jr, Temin S, Pao W, Aliff T, Brahmer J, et al. American Society of Clinical Oncology Clinical Practice Guideline update on chemotherapy for stage IV non-small-cell lung cancer. J Clin Oncol. 2009 Dec 20; 27(36):6251–66. [PubMed: 19917871]
6. D'Addario G, Felip E. Non-small-cell lung cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol. 2009 May; 20(Suppl 4):68–70. [PubMed: 19454467]
7. Azzoli CG, Temin S, Giaccone G. 2011 Focused Update of 2009 American Society of Clinical Oncology Clinical Practice Guideline Update on Chemotherapy for Stage IV Non-Small-Cell Lung Cancer. J Oncol Pract. 2012 Jan; 8(1):63–6. [PubMed: 22548014]
8. Mok TS, Wu YL, Yu CJ, Zhou C, Chen YM, Zhang L, et al. Randomized, placebo-controlled, phase II study of sequential erlotinib and chemotherapy as first-line treatment for advanced non-small-cell lung cancer. J Clin Oncol. 2009 Oct 20; 27(30):5080–7. [PubMed: 19738125]
9. Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2012 Mar; 13(3):239–46. [PubMed: 22285168]
10. Kwak EL, Bang YJ, Camidge DR, Shaw AT, Solomon B, Maki RG, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med. 2010 Oct 28; 363(18):1693–703. [PubMed: 20979469]
11. Hensing TA, Schell MJ, Lee JH, Socinski MA. Factors associated with the likelihood of receiving second line therapy for advanced non-small cell lung cancer. Lung Cancer. 2005 Feb; 47(2):253–9. [PubMed: 15639724]

12. Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med. 2006 Dec 14; 355(24): 2542–50. [PubMed: 17167137]

13. Pirker R, Pereira JR, Szczesna A, von Pawel J, Krzakowski M, Ramlau R, et al. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial. Lancet. 2009 May 2; 373(9674):1525–31. [PubMed: 19410716]

14. Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol. 2008 Jul 20; 26(21):3543–51. [PubMed: 18506025]

15. Smith IE, O'Brien ME, Talbot DC, Nicolson MC, Mansi JL, Hickish TF, et al. Duration of chemotherapy in advanced non-small-cell lung cancer: a randomized trial of three versus six courses of mitomycin, vinblastine, and cisplatin. J Clin Oncol. 2001 Mar 1; 19(5):1336–43. [PubMed: 11230476]

16. von Plessen C, Bergman B, Andresen O, Bremnes RM, Sundstrom S, Gilleryd M, et al. Palliative chemotherapy beyond three courses conveys no survival or consistent quality-of-life benefits in advanced non-small-cell lung cancer. Br J Cancer. 2006 Oct 23; 95(8):966–73. [PubMed: 17047644]

17. Park JO, Kim SW, Ahn JS, Suh C, Lee JS, Jang JS, et al. Phase III trial of two versus four additional cycles in patients who are nonprogressive after two cycles of platinum-based chemotherapy in non small-cell lung cancer. J Clin Oncol. 2007 Nov 20; 25(33):5233–9. [PubMed: 18024869]

18. Socinski MA, Schell MJ, Peterman A, Bakri K, Yates S, Gitten R, et al. Phase III trial comparing a defined duration of therapy versus continuous therapy followed by second-line therapy in advanced-stage IIIB/IV non-small-cell lung cancer. J Clin Oncol. 2002 Mar 1; 20(5):1335–43. [PubMed: 11870177]

19. Peters S, Adjei AA, Gridelli C, Reck M, Kerr K, Felip E, et al. Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2012; 23(suppl 7):vii56–vii64. 2012 October 1. [PubMed: 22997455]

20. Brodowicz T, Krzakowski M, Zwitter M, Tzekova V, Ramlau R, Ghilezan N, et al. Cisplatin and gemcitabine first-line chemotherapy followed by maintenance gemcitabine or best supportive care in advanced non-small cell lung cancer: a phase III trial. Lung Cancer. 2006 May; 52(2):155–63. [PubMed: 16569462]

21. Belani CP, Waterhouse DM, Ghazal H, Ramalingam SS, Bordoni R, Greenberg R, et al. Phase III study of maintenance gemcitabine (G) and best supportive care (BSC) versus BSC, following standard combination therapy with gemcitabine-carboplatin (G-Cb) for patients with advanced non-small cell lung cancer (NSCLC). ASCO Meeting Abstracts. 2010; 28(15_suppl):7506. 2010 June 14.

22. Belani CP, Barstis J, Perry MC, La Rocca RV, Nattam SR, Rinaldi D, et al. Multicenter, randomized trial for stage IIIB or IV non-small-cell lung cancer using weekly paclitaxel and carboplatin followed by maintenance weekly paclitaxel or observation. J Clin Oncol. 2003 Aug 1; 21(15):2933–9. [PubMed: 12885812]

23. Belani CP, Ramalingam S, Perry MC, LaRocca RV, Rinaldi D, Gable PS, et al. Randomized, phase III study of weekly paclitaxel in combination with carboplatin versus standard every-3-weeks administration of carboplatin and paclitaxel for patients with previously untreated advanced non-small-cell lung cancer. J Clin Oncol. 2008 Jan 20; 26(3):468–73. [PubMed: 18202422]

24. Gronberg BH, Bremnes RM, Flotten O, Amundsen T, Brunsvig PF, Hjelde HH, et al. Phase III study by the Norwegian lung cancer study group: pemetrexed plus carboplatin compared with gemcitabine plus carboplatin as first-line chemotherapy in advanced non-small-cell lung cancer. J Clin Oncol. 2009 Jul 1; 27(19):3217–24. [PubMed: 19433683]

25. Scagliotti G, Hanna N, Fossella F, Sugarman K, Blatter J, Peterson P, et al. The differential efficacy of pemetrexed according to NSCLC histology: a review of two Phase III studies. Oncologist. 2009 Mar; 14(3):253–63. [PubMed: 19221167]

26. Paz-Ares L, de Marinis F, Dediu M, Thomas M, Pujol JL, Bidoli P, et al. Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction

therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial. Lancet Oncol. 2012 Mar; 13(3):247–55. [PubMed: 22341744]

27. Paz-Ares L, De Marinis F, Dediu M, Thomas M, Pujol JL, Bidoli P, et al. PARAMOUNT: Final overall survival (OS) results of the phase III study of maintenance pemetrexed (pem) plus best supportive care (BSC) versus placebo (plb) plus BSC immediately following induction treatment with pem plus cisplatin (cis) for advanced nonsquamous (NS) non-small cell lung cancer (NSCLC). ASCO Meeting Abstracts. 2012; 30(15_suppl):LBA7507. 2012 May 30.
28. Johnson DH, Fehrenbacher L, Novotny WF, Herbst RS, Nemunaitis JJ, Jablons DM, et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol. 2004 Jun 1; 22(11):2184–91. [PubMed: 15169807]
29. Ramalingam SS, Dahlberg SE, Langer CJ, Gray R, Belani CP, Brahmer JR, et al. Outcomes for elderly, advanced-stage non small-cell lung cancer patients treated with bevacizumab in combination with carboplatin and paclitaxel: analysis of Eastern Cooperative Oncology Group Trial 4599. J Clin Oncol. 2008 Jan 1; 26(1):60–5. [PubMed: 18165641]
30. Dahlberg SE, Sandler AB, Brahmer JR, Schiller JH, Johnson DH. Clinical course of advanced non-small-cell lung cancer patients experiencing hypertension during treatment with bevacizumab in combination with carboplatin and paclitaxel on ECOG 4599. J Clin Oncol. 2010 Feb 20; 28(6): 949–54. [PubMed: 20085937]
31. Sandler AB, Schiller JH, Gray R, Dimery I, Brahmer J, Samant M, et al. Retrospective evaluation of the clinical and radiographic risk factors associated with severe pulmonary hemorrhage in first-line advanced, unresectable non-small-cell lung cancer treated with Carboplatin and Paclitaxel plus bevacizumab. J Clin Oncol. 2009 Mar 20; 27(9):1405–12. [PubMed: 19224857]
32. Reck M, von Pawel J, Zatloukal P, Ramlau R, Gorbounova V, Hirsh V, et al. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAil. J Clin Oncol. 2009 Mar 10; 27(8):1227–34. [PubMed: 19188680]
33. Patel JD, Hensing TA, Rademaker A, Hart EM, Blum MG, Milton DT, et al. Phase II study of pemetrexed and carboplatin plus bevacizumab with maintenance pemetrexed and bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer. J Clin Oncol. 2009 Jul 10; 27(20): 3284–9. [PubMed: 19433684]
34. Patel JD, Socinski MA, Garon EB, Reynolds CH, Spigel DR, Hermann RC, et al. A Randomized, Open-Label, Phase III, Superiority Study of Pemetrexed(Pem) + Carboplatin(Cb) + Bevacizumab(Bev) Followed by Maintenance Pem + Bev versus Paclitaxel (Pac)+Cb+Bev Followed by Maintenance Bev in Patients with Stage IIIB or IV Non-Squamous Non-Small Cell Lung Cancer (NS-NSCLC) 2012 Chicago Multidisciplinary Symposium in Thoracic Oncology. 2012
35. Pirker R, Pereira JR, von Pawel J, Krzakowski M, Ramlau R, Park K, et al. EGFR expression as a predictor of survival for first-line chemotherapy plus cetuximab in patients with advanced non-small-cell lung cancer: analysis of data from the phase 3 FLEX study. Lancet Oncol. 2012 Jan; 13(1):33–42. [PubMed: 22056021]
36. O'Byrne KJ, Gatzemeier U, Bondarenko I, Barrios C, Eschbach C, Martens UM, et al. Molecular biomarkers in non-small-cell lung cancer: a retrospective analysis of data from the phase 3 FLEX study. Lancet Oncol. 2011 Aug; 12(8):795–805. [PubMed: 21782507]
37. Lynch TJ, Patel T, Dreisbach L, McCleod M, Heim WJ, Hermann RC, et al. Cetuximab and first-line taxane/carboplatin chemotherapy in advanced non-small-cell lung cancer: results of the randomized multicenter phase III trial BMS099. J Clin Oncol. 2010 Feb 20; 28(6):911–7. [PubMed: 20100966]
38. Giaccone G, Herbst RS, Manegold C, Scagliotti G, Rosell R, Miller V, et al. Gefitinib in combination with gemcitabine and cisplatin in advanced non-small-cell lung cancer: a phase III trial--INTACT 1. J Clin Oncol. 2004 Mar 1; 22(5):777–84. [PubMed: 14990632]
39. Herbst RS, Giaccone G, Schiller JH, Natale RB, Miller V, Manegold C, et al. Gefitinib in combination with paclitaxel and carboplatin in advanced non-small-cell lung cancer: a phase III trial--INTACT 2. J Clin Oncol. 2004 Mar 1; 22(5):785–94. [PubMed: 14990633]

40. Gatzemeier U, Pluzanska A, Szczesna A, Kaukel E, Roubec J, De Rosa F, et al. Phase III study of erlotinib in combination with cisplatin and gemcitabine in advanced non-small-cell lung cancer: the Tarceva Lung Cancer Investigation Trial. J Clin Oncol. 2007 Apr 20; 25(12):1545–52. [PubMed: 17442998]

41. Herbst RS, Prager D, Hermann R, Fehrenbacher L, Johnson BE, Sandler A, et al. TRIBUTE: a phase III trial of erlotinib hydrochloride (OSI-774) combined with carboplatin and paclitaxel chemotherapy in advanced non-small-cell lung cancer. J Clin Oncol. 2005 Sep 1; 23(25):5892–9. [PubMed: 16043829]

42. Westeel V, Quoix E, Moro-Sibilot D, Mercier M, Breton JL, Debieuvre D, et al. Randomized study of maintenance vinorelbine in responders with advanced non-small-cell lung cancer. J Natl Cancer Inst. 2005 Apr 6; 97(7):499–506. [PubMed: 15812075]

43. Fidias PM, Dakhil SR, Lyss AP, Loesch DM, Waterhouse DM, Bromund JL, et al. Phase III study of immediate compared with delayed docetaxel after front-line therapy with gemcitabine plus carboplatin in advanced non-small-cell lung cancer. J Clin Oncol. 2009 Feb 1; 27(4):591–8. [PubMed: 19075278]

44. Ciuleanu T, Brodowicz T, Zielinski C, Kim JH, Krzakowski M, Laack E, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. Lancet. 2009 Oct 24; 374(9699):1432–40. [PubMed: 19767093]

45. Hanna N, Shepherd FA, Fossella FV, Pereira JR, De Marinis F, von Pawel J, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol. 2004 May 1; 22(9):1589–97. [PubMed: 15117980]

46. Cappuzzo F, Ciuleanu T, Stelmakh L, Cicenas S, Szczesna A, Juhasz E, et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. Lancet Oncol. 2010 Jun; 11(6):521–9. [PubMed: 20493771]

47. Fukuoka M, Wu YL, Thongprasert S, Sunpaweravong P, Leong SS, Sriuranpong V, et al. Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS). J Clin Oncol. 2011 Jul 20; 29(21):2866–74. [PubMed: 21670455]

48. Zhou C, Wu YL, Chen G, Feng J, Liu XQ, Wang C, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol. 2011 Aug; 12(8):735–42. [PubMed: 21783417]

49. Perol M, Chouaid C, Perol D, Barlesi F, Gervais R, Westeel V, et al. Randomized, phase III study of gemcitabine or erlotinib maintenance therapy versus observation, with predefined second-line treatment, after cisplatin-gemcitabine induction chemotherapy in advanced non-small-cell lung cancer. J Clin Oncol. 2012 Oct 1; 30(28):3516–24. [PubMed: 22949150]

50. Takeda K, Hida T, Sato T, Ando M, Seto T, Satouchi M, et al. Randomized phase III trial of platinum-doublet chemotherapy followed by gefitinib compared with continued platinum-doublet chemotherapy in Japanese patients with advanced non-small-cell lung cancer: results of a west Japan thoracic oncology group trial (WJTOG0203). J Clin Oncol. 2010 Feb 10; 28(5):753–60. [PubMed: 20038730]

51. Zhang L, Ma S, Song X, Han B, Cheng Y, Huang C, et al. Gefitinib versus placebo as maintenance therapy in patients with locally advanced or metastatic non-small-cell lung cancer (INFORM; C-TONG 0804): a multicentre, double-blind randomised phase 3 trial. Lancet Oncol. 2012 May; 13(5):466–75. [PubMed: 22512843]

52. Gaafar RM, Surmont VF, Scagliotti GV, Van Klaveren RJ, Papamichael D, Welch JJ, et al. A double-blind, randomised, placebo-controlled phase III intergroup study of gefitinib in patients with advanced NSCLC, non-progressing after first line platinum-based chemotherapy (EORTC 08021/ILCP 01/03). Eur J Cancer. 2011 Oct; 47(15):2331–40. [PubMed: 21802939]

53. Miller VA, O'Connor P, Soh C, Kabbinavar F. for the ATLAS Investigators. A randomized, double-blind, placebo-controlled, phase IIIb trial (ATLAS) comparing bevacizumab (B) therapy with or without erlotinib (E) after completion of chemotherapy with B for first-line treatment of

locally advanced, recurrent, or metastatic non-small cell lung cancer (NSCLC). ASCO Meeting Abstracts. 2009; 27(18S):LBA8002. 2009 June 18.

54. Lima JP, dos Santos LV, Sasse EC, Sasse AD. Optimal duration of first-line chemotherapy for advanced non-small cell lung cancer: a systematic review with meta-analysis. Eur J Cancer. 2009 Mar; 45(4):601–7. [PubMed: 19111457]
55. Buccheri GF, Ferrigno D, Curcio A, Vola F, Rosso A. Continuation of chemotherapy versus supportive care alone in patients with inoperable non-small cell lung cancer and stable disease after two or three cycles of MACC. Results of a randomized prospective study. Cancer. 1989 Feb 1; 63(3):428–32. [PubMed: 2536288]
56. Soon YY, Stockler MR, Askie LM, Boyer MJ. Duration of chemotherapy for advanced non-small-cell lung cancer: a systematic review and meta-analysis of randomized trials. J Clin Oncol. 2009 Jul 10; 27(20):3277–83. [PubMed: 19470938]
57. Behera M, Owonikoko TK, Chen Z, Kono SA, Khuri FR, Belani CP, et al. Single-agent maintenance therapy for advanced-stage non-small cell lung cancer: A meta-analysis. ASCO Meeting Abstracts. 2011; 29(15_suppl):7553. 2011 June 9.
58. Zhang X, Zang J, Xu J, Bai C, Qin Y, Liu K, et al. Maintenance therapy with continuous or switch strategy in advanced non-small cell lung cancer: a systematic review and meta-analysis. Chest. 2011 Jul; 140(1):117–26. [PubMed: 21436247]
59. Gervais R, Hainsworth JD, Blais N, Besse B, Laskin J, Hamm JT, et al. Phase II study of sunitinib as maintenance therapy in patients with locally advanced or metastatic non-small cell lung cancer. Lung Cancer. 2011; 74(3):474–80. [PubMed: 21680048]
60. De Pas T, Giovannini M, Rescigno M, Catania C, Toffalorio F, Spitaleri G, et al. Vaccines in non-small cell lung cancer: Rationale, combination strategies and update on clinical trials. Crit Rev Oncol Hematol. 2012 Feb 24.
61. Lynch TJ, Bondarenko I, Luft A, Serwatowski P, Barlesi F, Chacko R, et al. Ipilimumab in Combination With Paclitaxel and Carboplatin As First-Line Treatment in Stage IIIB/IV Non-Small-Cell Lung Cancer: Results From a Randomized, Double-Blind, Multicenter Phase II Study. J Clin Oncol. 2012 Jun 10; 30(17):2046–54. [PubMed: 22547592]
62. Nemunaitis J, Dillman RO, Schwarzenberger PO, Senzer N, Cunningham C, Cutler J, et al. Phase II study of belagenpumatucel-L, a transforming growth factor beta-2 antisense gene-modified allogeneic tumor cell vaccine in non-small-cell lung cancer. J Clin Oncol. 2006 Oct 10; 24(29): 4721–30. [PubMed: 16966690]
63. Quoix E, Ramlau R, Westeel V, Papai Z, Madroszyk A, Riviere A, et al. Therapeutic vaccination with TG4010 and first-line chemotherapy in advanced non-small-cell lung cancer: a controlled phase 2B trial. Lancet Oncol. 2011 Nov; 12(12):1125–33. [PubMed: 22019520]
64. Neninger Vinageras E, de la Torre A, Osorio Rodriguez M, Catala Ferrer M, Bravo I, Mendoza del Pino M, et al. Phase II randomized controlled trial of an epidermal growth factor vaccine in advanced non-small-cell lung cancer. J Clin Oncol. 2008 Mar 20; 26(9):1452–8. [PubMed: 18349395]
65. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med. 2012 Jun 28; 366(26):2443–54. [PubMed: 22658127]
66. Brahmer JR, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, Hwu P, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med. 2012 Jun 28; 366(26):2455–65. [PubMed: 22658128]

Table 1

Continuation maintenance: completed phase III trials

TRIALS DIRECTLY INVESTIGATING CONTINUATION MAINTENANCE*

YEAR	AUTHORS	DESIGN	PRIMARY OUTCOME	RESULTS	COMMENTS
2006	Brodowicz, et al. [20]	Cisplatin/gemcitabine × 4 cycles → gemcitabine vs. BSC (n-352)	TTP	TTP : 6.6 vs. 5 mos. (p<0.0001) OS: 13 vs. 11 mos. (p=0.195)	
2010	Belani, et al.[21]	Carboplatin/gemcitabine ×4 cycles → gemcitabine vs. BSC (n=519)	OS	PFS: 3.9 vs. 3.8 mos. (p=0.575) OS: 8 vs. 9.3 mos. (p=0.838)	
2010	Perol, et al. [22]	Cisplatin/gemcitabine × 4 cycles → gemcitabine vs. BSC (n=464)	PFS	PFS: 3.8 vs. 1.9 mos. (p=0.001) OS: NR (HR = 0.86; 95% CI 0.66-1.12)	
2012	Paz Arez, et al. (PARAMOUNT)[27,28]	Cisplatin/pemetrexed × 4 cycles → pemetrexed vs. BSC/placebo (n=539)	PFS	PFS: 4.1 vs. 2.8 mos. (p=<0.0001) OS: 13.9 vs. 11.0 mos. (p=0.0195),	Nonsquamous histology only

TRIALS INDIRECTLY INVESTIGATING CONTINUATION MAINTENANCE†

YEAR	AUTHORS	DESIGN	PRIMARY OUTCOME	RESULTS	COMMENTS
2003	Belani, et al.[23]	Paclitaxel/carboplatin (3 seperate regimens) → paclitaxel vs. BSC (n=401)	TTP	TTP: 38 vs. 49 wks. (p=NR) OS: 75 vs. 60 wks. (p=NR)	
2006	Sandler, et al. (ECOG 4399)[12]	Paclitaxel/carboplatin/bevacizumab → bevacizumab (n=878)	OS	PFS: 6.2 vs. 4.5 mos. (P<0.001) OS: 12.3 vs. 10.3 mos. (p=0.03)	
2008	Belani, et al.[24]	Weekly vs. standard (Q 3 week) paclitaxel/ carboplatin→ weekly paclitaxel (n=444)	OS	TTP, weekly: 33 (maintence) vs. 12wks. (no maintence) (p=NR) TTP, Q 3 week: 29 (maintenance) vs. 11wks. (no maintence) (p=NR) OS: 39 (weekly) vs. 43 wks. (q3 weeks) (p=NR)	No formal best supportive care/ placebo arm
2009	Reck, et al.(AVAil)[33]	Carboplatin/gemcitabine + 15mg/kg vs. 7.5mg/kg bevacizumab vs. placebo → bevacizumab (n=1043)	PFS	PFS: 6.5 vs. 6.7 vs. 6.1 mos. (p= 0.3, 0.003) OS: NR	
2009	Priker, et al. (FLEX)[13]	Cisplatin/vinorelbine + cetuximab →weekly cetuximab (n= 1125)	OS	PFS: 4.8 vs. 4.8 mos. (p=0.39) OS: 11.3 vs. 10.1 mos. (p=0.044)	
2010	Lynch, et al. (BMS009)[36]	Carboplatin/paclitaxel or docetaxel + cetuximab →weekly cetuximab (n= 676)	PFS	PFS: 4.4 vs. 4.24 mos. (p=0.236) OS: 9.69 vs. 8.38 mos. (p=0.161)	

2012	Patel, et al. (PointBreak)[35]	Paclitaxel/carboplatin/bevacizumab × 4 cycles → bevacizumab vs. Pemetrexed/carboplatin/ bevacizumab × 4 cycles → bevacizumab + pemetrexed (n= 1259)	OS	PFS: 6.9 vs. 8.6 mos. (p=NR) OS: 15.7 vs. 17.7 mos. (P=NR)	Non compartive analysis of maintenance arms

Table II

Switch maintenance: completed phase III trials

CONVENTIONAL CHEMOTHERAPY				
YEAR	**AUTHORS**	**DESIGN**	**PRIMARY OUTCOME**	**RESULTS**
2005	Westeel, et al.[41]	Mitomycin/ifosfamide/cisplatin × 4 cycles → vinorelbine × 6 mos. (n= 573)	OS	PFS: 5 vs. 3 mos. (p=0.11) OS: 12.3 vs. 12. 3 mos. (p=0.65)
2009	Fidias, et al.[42]	Gemcitabine/carboplatin × 4 cycles → immediate vs. delayed docetaxel (n=566)	OS	PFS: 5.7 vs. 2.7 mos. (p=0.001) OS: 12.3 vs. 9.7 mos. (p=0.853)
2009	Cilueanu, et al.[43]	Platinum doublet × 4 cycles → pemetrexed vs. placebo (n=663)	PFS	PFS: 4.3 vs. 2.6 mos. (p< 0.0001) OS: 13.4 vs. 10.6 mos. (p=0.012)
TARGETED CHEMOTHERAPY				
YEAR	**AUTHORS**	**DESIGN**	**PRIMARY OUTCOME**	**RESULTS**
2009	Miller, et al. (ATLAS)[51]	Platinum doublet + bevacizumab(bev) ×4 cycles → bev vs. bev + erlotinib (n=1160)	PFS	PFS: 4.8 vs. 3.7 mos. (p=0.0012) OS: 15.9 vs. 13.9 mos. (p=0.27)
2010	Cappuzzo, et al. (SATURN)[45]	Platinum doublet × 4 cycles → erlotinib vs. placebo (n=1949)	PFS	PFS: 12.3 vs. 11.1 wks (P<0.0001) OS: 12 vs. 11 mos. (p=0.0088)
2010	Perol, et al.[22]	Cisplatin/gemcitabine × 4 cycles → Erlotinib vs. BSC (n=464)	PFS	PFS: 3.7 vs. 2.1 mos. (p=0.001) OS: 11.8 vs. 10.7 mos. (P> 0.05)
2010	Takeda, et al.[48]	Platinum doublet × 3 cycles → gefitinib vs. 3 additional cycles platinum doublet (n=604)	OS	PFS: 4.6 vs. 4.3 mos. (p<0.001) OS: 13.7 vs. 12.9 mos. (p=0.11)
2011	Gaafar, et al.[50]	Platinum doublet × 4 cycles → gefitinib vs. placebo (n=173)	OS	PFS: 4.1 vs. 2.9 mos. (p=0.0015) OS: 10.9 vs. 94. mos. (p=0.204)
2012	Zhang, et al.[49]	Platinum doublet ×4 cycles → gefitinib vs. placebo (n=296)	PFS	PFS: 4.8 vs. 2.6 mos. (p<0.0001) OS: 18.7 vs. 16.9 mos. (p=0.26)

Table III

Maintenance trials: ongoing phase III trials

CONVENTIONAL CHEMOTHERAPY				
TRIAL / NCT NUMBER	**DESIGN**	**PRIMARY OUTCOME**	**ESTIMATED ENROLMENT**	**ESTIMATED COMPLETION DATE**
AVAPERL1 / NCT00961415	Cisplatin/pemetrexed/bevacizumab × 4 cycles→ bevacizumab vs.	PFS	348	May 2012
	Cisplatin/pemetrexed/bevicizumab × 4 cycles → bevacizumab + pemetrexed			
NCT00948675	Paclitaxel/carboplatin/bevacizumab × 4 cycles→bevacizumab vs.	PFS	360	June 2013
	Paclitaxel/carboplatin × 4 cycles → pemetrexed			
ECOG 5508 / NCT01107626	Carboplatin/paclitaxel/bevacizumab × 4 cycles→ bevacizumab vs.	OS	1282	October 2012
	Carboplatin/paclitaxel/bevacizumab × 4 cycles → pemetrexed vs.			
	Carboplatin/paclitaxel/bevacizumab × 4 cycles → pemetrexed + bevacizumab			
TARGETED CHEMOTHERAPY				
TRIAL / NCT NUMBER	**DESIGN**	**PRIMARY OUTCOME**	**ESTIMATED ENROLLMENT**	**ESTIMATED COMPLETION DATE**
CALGB 30607 / NCT00693992	Platinum doublet × 4 cycles → sunitinib vs.placebo	PFS	244	January 2010
SWOG 0819 / NCT00946712	Paclitaxel/carboplatin/bevacizumab × 6 cycles→ bevacizumab vs.	OS	1546	June 2012
	Paclitaxel/carboplatin/bevacizumab × 6 cycles → bevacizumab + weekly cetuximab			
MAINTENANCE IMMUNOTHERAPY				
TRIAL / NCT NUMBER	**DESIGN**	**PRIMARY OUTCOME**	**ESTIMATED ENROLLMENT**	**ESTIMATED COMPLETION DATE**
NCT1285609	Paclitaxel/carboplatin × 6 cycles → ipilumimab vs. placebo	OS	920	June 2016
STOP / NCT00676507	Platinum doublet up to 6 cycles → belagenpumatucel - L vs. placebo	OS	506	October 2012
NCT01383148	Platinum doublet to 6 cycles → TG410 vs. placebo	OS	1000	December 2016
NCT00516685	Induction chemotherapy (not specified)→ rHuEGF vs. BSC	OS	230	NR