Metastatic Non–Small Cell Lung Cancer Management: Novel Targets and Recent Clinical Advances

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Abstract: Lung cancer continues to be the most common cause of cancer-related mortality in the United States and other developed countries. The most common subtype is non–small cell lung cancer (NSCLC). Within NSCLC, we are discovering remarkable molecular heterogeneity. Most current actionable mutations have been identified in patients with adenocarcinoma histology, but now new mutations are being discovered in squamous cell histology patients as well. This molecular heterogeneity provides an opportunity for clinical trials to exploit various candidate oncogene-addicted pathways in NSCLC. This article focuses on 2 shifting paradigms in NSCLC management: the recent advances in targeted therapy and maintenance treatment.

Introduction

We are in the midst of an exciting time in the treatment of non–small cell lung cancer (NSCLC), with remarkable recent advances in management. Treatment is increasingly being driven by molecular characteristics. Drugs targeting driver mutations have greatly improved outcomes in the selected patients who harbor these mutations, such as erlotinib (Tarceva, Genentech/OSI) in NSCLC with epidermal growth factor receptor (EGFR) activating mutations and, most recently, crizotinib (PF-02341066, Pfizer) in NSCLC with an anaplastic lymphoma kinase (ALK) translocation. The search for other important driver mutations and drugs to target these dysregulated pathways is ongoing (Table 1).

The ability to link molecular markers to targeted treatments, both in the trial setting and as standard of care for patients with ALK and EGFR activating mutations, has radically altered our approach to therapy (Table 2). Molecular profiling is important for current treatment and for future advances in lung cancer. For example, the Lung Cancer Mutation Consortium, a group of 14 institutions, recently presented data profiling tissue from NSCLC adenocarcinoma for specific mutations and linked them to relevant targeted treatment with either approved drugs or clinical trials.[1] A similar analysis of a smaller group of squamous cell histology patients indicates that identification of driver mutations is also feasible in that subset of NSCLC patients.[2] The BATTLE

Table 1. Biomarkers and Potential Corresponding Specific Therapy by Molecular Subtype: Ongoing Investigations

Molecular Marker	Drug(s)	Mechanism
EGFR T790M resistance mutation	Afatinib+cetuximab	Irreversible EGFR-TKI + monoclonal EGFR antibody
EGFR FISH amplification	Cetuximab	Monoclonal anti-EGFR antibody
ALK translocation	Retaspimycin/ganetespib	Hsp-90 inhibitor
ROS1 translocation	Crizotinib	ALK/MET/ROS1 inhibitor
BRAF mutation	GSK2118436	BRAF inhibitor/MEK inhibitor
K-ras mutation	Sorafenib	Pan-TKI/raf inhibitor
	Tivantinib (ARQ197)	c-MET inhibitor
MET IHC positive	Onartuzumab (MetMab)	Anti-MET monoclonal antibody
DDR2 mutation	Dasatinib	Src inhibitor, pan-TKI
PI3K mutation	BKM120	PI3K TKI
	BEZ235	Dual PI3K/mTOR inhibitor
FGFR1 amplification	FGFR1 monoclonal antibodies/FGFR-TKIs	

mTOR= mammalian target of rapamycin.

Table 2. FDA-Approved Targeted Therapies and Major Recent Trial Results That Led to Their Approval

Molecular Marker	Trial	Drug	PFS
EGFR activating mutation	IPASS[4]	Gefitinib vs chemo	9.5 vs 6.3 months (HR, 0.48)
	NEJ-002[6]	Gefitinib vs chemo	10.8 vs 5.4 months (HR, 0.30)
	EURTAC[7]	Erlotinib vs chemo	9.7 vs 5.2 months (HR, 0.49)
ALK translocation	Kwak et al[23]	Crizotinib	6.4 months

EURTAC=European Erlotinib Versus Chemotherapy; FDA=Food and Drug Administration; HR=hazard ratio; IPASS=Iressa Pan-Asia Study; NEJ=North-East Japan; PFS=progression-free survival.

(Biomarker-Integrated Approaches of Targeted Therapy for Lung Cancer Elimination) trial illustrates an exciting new approach to NSCLC clinical trials. This study demonstrated the feasibility of obtaining repeat biopsies after initial progression in heavily pretreated patients to guide therapy. The study adaptively randomized patients based on biomarker results from pretreatment biopsies in an attempt to determine subsets of patients who may benefit from specific targeted treatments.[3]

In addition to targeted treatments, maintenance treatment of NSCLC has also gained increasing popularity as a new treatment paradigm in NSCLC. This review is intended as a summary of the most relevant recent advances in metastatic NSCLC treatment, with a focus on maintenance therapy, targeted agents, and novel immunotherapeutics.

Targeting EGFR in Patients With EGFR Activating Mutations

EGFR activating mutations are found in approximately 15–20% of lung adenocarcinoma patients, with a higher frequency in never-smokers, Asians, and women.[1,4] However, lung adenocarcinomas from former and current smokers may also contain an EGFR activating mutation, with recent data showing that approximately 6% of

adenocarcinomas from current smokers and 15% from former smokers harbor an EGFR activating mutation.[5]

EGFR tyrosine kinase inhibitors (EGFR-TKIs) are now the standard of care for first-line treatment of patients whose tumors have an EGFR activating mutation. A prespecified subset analysis of the landmark IPASS (Iressa Pan-Asia Study) first showed that the EGFR-TKI gefitinib (Iressa, AstraZeneca) prolongs progression-free survival (PFS) compared to first-line chemotherapy in Asian patients who harbor an activating EGFR mutation.[4] Results from a Japanese trial confirmed the PFS benefit of EGFR-TKIs compared to platinum doublet therapy.[6] The EURTAC (European Erlotinib Versus Chemotherapy) trial confirmed this PFS benefit in a predominantly European population.[7] The lack of overall survival (OS) benefit seen throughout these trials, despite prolongation of PFS, is most likely secondary to patient crossover, with most patients eventually going on to receive an EGFR-TKI.

Unfortunately, resistance develops in most EGFR mutant tumors, with a median PFS of 10.8 months in the Japanese study, 9.5 months in the IPASS study, and 9.7 months in the European study. The 2 main mechanisms of resistance to EGFR-TKIs include the T790M mutation, which represents about 50% of all resistance mutations, and MET amplification, which may represent up to 20%.[8] The T790M mutation changes the conformation of the EGFR receptor and sterically hinders the binding of the EGFR-TKI.[9] MET amplification leads to EGFR independent activation of the downstream PI3K-AKT pathway.[10] Discovery of other resistance mechanisms is ongoing.

Numerous efforts to rationally combine other targeted agents to overcome resistance to EGFR-TKI are under way. Currently, there is promising phase II data combining the irreversible EGFR-TKI afatinib and the EGFR antibody cetuximab (Erbitux, ImClone/Bristol-Myers Squibb). In a phase II trial, afatinib combined with cetuximab in 61 patients with acquired EGFR resistance produced a 100% disease control rate and a high partial response (PR) rate, which was achieved by approximately one-third of patients with a T790M mutation.[11]

Aside from novel therapeutics, patients who become resistant to EGFR-TKI may benefit in the future from re-exposure to an EGFR-TKI. After time off an EGFR-TKI, the patient may be resensitized to EGFR inhibition from regrowth of a fraction of nonresistant EGFR-mutated tumor cells. A small retrospective study showed a 73% disease control rate in 11 patients retreated with gefitinib after initial treatment failure.[12]

Debate exists over whether EGFR-TKIs should be combined with chemotherapy, and whether they should be continued beyond progression. Early clinical trials combining EGFR-TKIs with chemotherapy were negative in an unselected population.[13,14] The case for continuing a TKI in patients with an EGFR mutation is based on a more rapid progression noted in some patients taken off EGFR-TKIs after initial progression.[15] If an EGFR activating mutation is discovered during first-line chemotherapy, the most recent National Comprehensive Cancer Network (NCCN) guidelines suggest adding erlotinib as a category 2B recommendation. However, there is no consensus on this point and many providers will continue the chemotherapy until progression, then switch to the EGFR-TKI or add it as maintenance therapy. The CALGB (Cancer and Leukemia Group B) trial, which looked at combined chemotherapy and erlotinib, did not demonstrate a survival benefit for the combination, even in patients with EGFR activating mutations.[16]

Targeting EGFR in an Unselected NSCLC Population

In contrast to EGFR-TKIs, which function through intracellular inhibition of the EGFR tyrosine kinase domain, cetuximab is a monoclonal antibody that binds to the extracellular domain of EGFR. The FLEX (First-Line Erbitux in Lung Cancer) study assigned 1,125 patients with NSCLC to either cisplatin and vinorelbine or cisplatin, vinorelbine, and cetuximab.[17] Median overall survival was 1.2 months longer in the patients receiving cetuximab (P=.044). Based on a subset analysis, benefit seemed greatest in squamous cell histology patients (hazard ratio [HR], 0.80). However, when added to carboplatin and paclitaxel, cetuximab did not increase progression-free survival (PFS) or overall survival (OS), despite a higher overall response rate (ORR).[18]

With mixed data regarding the benefit of cetuximab and OS, identifying biomarkers to select patients who preferentially benefit from cetuximab is of great interest. A subgroup analysis of the FLEX study suggested that patients who had a first-cycle rash might benefit more from cetuximab, with an OS of 15 months versus 8.8 months in patients who did not have a first-cycle rash.[19] Another potential biomarker is EGFR expression assayed by immunohistochemistry (IHC). In a retrospective analysis, an EGFR IHC score was generated from a percentage of cancer cells that expressed EGFR with a range of 0–300. Dichotomizing patients into IHC scores greater or less than 200, the median OS in the high-expression group treated with cetuximab plus chemotherapy was 12 months, compared with 9.6 months in high-expression patients treated with chemotherapy alone (HR, 0.73; P=.011).[20] Although cetuximab is not approved by the US Food and Drug Administration (FDA) for the treatment of NSCLC, these selection criteria may lead to a role for the drug in subsets of NSCLC patients.

ALK

Since the ALK oncogenic fusion protein was identified in a NSCLC patient in 2007,[21] there has been rapid development of agents targeting ALK. In unselected NSCLC patients, 2–7% harbor an ALK gene rearrangement. In lung adenocarcinoma, ALK's fusion partner, EML4, lies upstream on chromosome 2. Nine different inversions of EML4-ALK that cause constitutive tyrosine kinase activation have been identified.[22]

Crizotinib (Xalkori, Pfizer), an oral tyrosine kinase inhibitor, was initially developed as a MET inhibitor, but activity in a NSCLC patient who was later found to have an ALK gene rearrangement spurred its development in ALK-positive NSCLC. In a phase I/II trial of these patients, crizotinib as second-line treatment led to a response in 57% of patients and disease stability in 33% of patients.[23] Resistance eventually developed, with a mean PFS of 14 weeks and a 6-month PFS achieved by 27.2% of patients. Mechanisms of resistance to ALK inhibition are an area of active investigation. Like the T790M EGFR mutation, some resistance to ALK inhibition is mediated by gatekeeper mutations that alter the ATP binding site.[24] Crizotinib has recently been given accelerated approval by the FDA in metastatic NSCLC patients harboring an ALK translocation along with a companion fluorescent in situ hybridization (FISH) diagnostic test. Approval is contingent upon the results of the ongoing phase III PROFILE 1007 (A Phase III Trial of Crizotinib Versus Standard of Care in Patients With Advanced Non–Small-Cell Lung Cancer With a Specific Alteration of the Anaplastic Lymphoma Kinase Gene) trial of crizotinib versus physician's choice of pemetrexed (Alimta, Eli Lilly) or docetaxel in the second-line setting and beyond.

NSCLC patients with nonsquamous histology preferentially benefit from pemetrexed over gemcitabine. The inverse is true for patients with squamous cell histology who do not appear to derive benefit from pemetrexed. This was shown in a phase III study, where nonsquamous histology patients who received cisplatin and pemetrexed had improved OS compared with cisplatin and gemcitabine in the first-line setting.[25] Within NSCLC-adenocarcinoma patients, data are emerging that patients who harbor an ALK translocation may have an improved response to pemetrexed. In a retrospective, exploratory analysis, patients with an ALK gene rearrangement had a prolonged PFS (9 months) compared with patients with a K-ras mutation (7 months), EGFR activating mutation (5.5 months), or neither of these mutations (4 months).[26] Another retrospective analysis showed increased time to progression (TTP) and ORR in patients whose tumors harbored an ALK translocation, compared with EGFR mutant and wild-type tumors (TTP 9.4 months vs 1.4 months vs 2.9 months, respectively).[27] A hypothesis for the differential effect of pemetrexed in ALK-positive tumors includes increased response to lower thymidylate synthase levels as well as differential expression of other pathways involved in DNA base biosynthesis.[28] These intriguing results await further preclinical studies and clinical validation in a prospective fashion.

Efforts to overcome resistance to crizotinib are ongoing, and irreversible ALK inhibitors are currently in development. Another promising class of drugs for ALK-positive patients is heat-shock protein-90 (HSP90) inhibitors. In a crizotinib-resistant ALK-positive cell line, HSP90 inhibition overcomes crizotinib resistance and suppresses phosphorylation of ALK, AKT, and ERK, inducing marked apoptosis.[29] In an open-label, phase II study of the HSP90 inhibitor retaspimycin (IPI-504, Infinity/MedImmune), 96 patients were enrolled with a primary endpoint of 16-week PFS. Among the 76 evaluable patients, the PFS rate at 16 weeks was 24.1%, with a 5.3% ORR and 54% disease stability rate. All objective responders were patients with ALK gene rearrangements.[30] Ganetespib (STA-9090) is another HSP90 inhibitor with promising early phase data. A phase IIb/III trial of ganetespib and docetaxel is currently ongoing.

K-ras

K-ras is the most frequent mutation found among NSCLC patients with adenocarcinoma. Despite being the first driver mutation discovered in NSCLC, therapies targeting K-ras have been less successful than those targeting EGFR and ALK thus far. ARQ197 (tivantinib), a noncompetitive inhibitor of c-MET, may have some activity in patients with K-ras mutations. In a randomized phase II trial of patients treated with erlotinib plus ARQ197 versus erlotinib alone, PFS was 3.7 months versus 2.2 months, just approaching statistical significance. In a subset analysis, K-ras mutant patients derived the most benefit (HR, 0.18), but the total number of patients studied with K-ras mutations was small. The phase III MARQUEE (Met Inhibitor ARQ 197 Plus Erlotinib vs Erlotinib Plus Placebo in NSCLC) trial is comparing erlotinib plus ARQ197 to chemotherapy in nonsquamous metastatic patients, and is stratified by EGFR and K-ras mutation status.

Although it is being combined with ARQ197, erlotinib alone may be less effective as a single-agent, second-line treatment of NSCLC with K-ras mutations. A recent molecular marker analysis of the SATURN (Sequential Tarceva in Unresectable NSCLC) trial, which showed a modest OS benefit of erlotinib maintenance in unselected patients, indicated that K-ras mutation status predicted decreased benefit from erlotinib treatment.[31] The recently published BATTLE trial also showed that patients with

K-ras mutations had a poorer 8-week disease control rate with erlotinib than with sorafenib (79% vs 14%; *P*=.016). A trend towards increased 8-week disease control rate in patients with K-ras mutant tumors treated with sorafenib compared with the other treatments in the BATTLE study (61% vs 32%; *P*=.11) may also signal preferential benefit of sorafenib in K-ras tumors.

MET

MET is a tyrosine kinase receptor that binds hepatocyte growth factor leading to prosurvival, motility, and proliferation signals.[32] Overexpression is associated with worse prognosis in several tumor types, including NSCLC. Promising data were presented at the 2011 American Society of Clinical Oncology (ASCO) meeting on a phase II trial combining erlotinib with onartuzumab (MetMab, Genentech), a monovalent antibody that inhibits hepatocyte growth factor–mediated stimulation of the MET receptor.[33]

In a phase II trial, 137 patients were randomized to receive erlotinib plus placebo or erlotinib plus onartuzumab, with crossover allowed upon progression. No difference in PFS or OS was noted in the intent-to-treat population. However, significant improvement in PFS and OS was noted in the MET IHC-positive patients. Trends toward harm were noted in the MET IHC-negative patients. Benefit in MET IHC-positive patients was noted even in EGFR wild-type patients treated with erlotinib and onartuzumab. Based on these phase II results, a phase III trial is under way in MET IHC-positive patients, as is a phase II trial combining chemotherapy with onartuzumab.

PI3-Kinase (PI3K)/BRAF

There are several less common mutations in NSCLC patients. PI3K mutations have been identified in several tumor types, but only approximately 2% of NSCLC patients.[34] Both adenocarcinoma and squamous cell histology can harbor these mutations, and PI3K mutations can coexist with EGFR mutations.[35] BKM120 is a competitive inhibitor of PI3K that is currently being studied in clinical trials. BEZ235 is a dual competitive inhibitor of PI3K and mTOR that recently completed phase I trials.

Approximately 2% of lung adenocarcinoma patients harbor a BRAF mutation,[1] and they are less likely to harbor the V600E mutation than melanoma patients.[36-38] Ongoing trials are looking at BRAF inhibitors in NSCLC patients with BRAF mutations. BRAF mutations have also been shown to predict sensitivity to MEK inhibition.[39] There are several other mutations that occur at lower frequency in NSCLC patients, including HER2, MEK, and AKT. However, significant benefit from targeting these mutations has yet to be seen, and is the subject of ongoing clinical trials.

ROS1

ROS1 translocations are a newly discovered driver mutation in NSCLC. They are estimated to occur in approximately 2% of lung adenocarcinoma, and patient characteristics are similar to ALK and EGFR (nonsmokers, lung adenocarcinoma histology, and younger patients).[40] Recent preclinical data indicate sensitivity to ALK inhibitors, including crizotinib, and crizotinib was shown to dramatically shrink tumor size in at least 1 patient harboring an ROS1 translocation.[40]

Squamous Cell Histology

Development of effective targeted treatments for squamous cell histology has lagged behind its adenocarcinoma counterpart, but is now the subject of active investigation. The fibroblast growth factor receptor (FGFR) has been identified as a potential target in squamous cell histology lung cancer. FGFRs are a class of membrane-bound tyrosine kinase receptors that bind to FGF, leading to activation of downstream growth and survival signals. FGFR1 is amplified in approximately 3% of lung adenocarcinoma patients and in 21% of squamous cell lung cancer patients, with inhibition of FGFR1 leading to cell death in preclinical studies.[41,42] Early phase trials targeting FGFR with monoclonal antibodies and tyrosine kinase inhibitors are in progress.

The discoidin domain receptor 2 (DDR2) is another promising target in squamous cell histology lung cancer. When activated, DDR2 promotes cell migration, proliferation, and survival.[43] It is mutated in approximately 4% of squamous cell lung cancer patients, with preclinical and early clinical data indicating sensitivity to dasatinib (Sprycel, Bristol-Myers Squibb).[44] A phase II trial with dasatinib in advanced squamous cell histology lung cancer patients is currently recruiting participants.

Nonvaccine Immunologic Therapies in Metastatic NSCLC

Exciting developments are occurring using immunotherapeutic agents in NSCLC. There are several vaccine studies, mainly in nonmetastatic patients, that have been expertly covered in several recent reviews.[45]

Ipilumumab (Yervoy, Bristol-Myers Squibb), a fully humanized IgG1 monoclonal antibody, augments

Table 3. Progression-Free and Overall Survival Results in Recent Major Continuation Maintenance Trials in NSCLC

Continuation Maintenance	Trial	PFS (months)	OS (months)
Bevacizumab	E4599[66]	6.2 vs 4.5*	12.3 vs 10.3*
	AVAiL[67]	6.7 vs 6.1*	13.6 vs 13.1
Gemcitabine	Belani et al[58]	7.4 vs 7.7	8 vs 9.3
	IFCT[57]	3.8 vs 1.9*	12.1 vs 10.8
Pemetrexed	PARAMOUNT[59]	3.9 vs 2.6*	Not mature
Pemetrexed and Bevacizumab versus Bevacizumab	AVAPERL[60]	10.2 vs 6.6*	Not mature

AVAiL=Avastin in Lung Cancer; AVAPERL=A Study of Avastin (Bevacizumab) With or Without Pemetrexed as Maintenance Therapy After Avastin in First Line in Patients With Non-Squamous Non-Small Cell Lung Cancer; IFCT= Intergroupe Francophone de Cancérologie Thoracique; NSCLC=non–small cell lung cancer; OS=overall survival; PARAMOUNT=Phase III Study of Maintenance Pemetrexed (pem) Plus Best Supportive Care (bsc) Versus Placebo Plus bsc Immediately Following Induction Treatment With Pem Plus Cisplatin for Advanced Nonsquamous Non-Small Cell Lung Cancer (NSCLC); PFS=progression-free survival.
*Statistically significant (P<.05).

Table 4. Progression-Free and Overall Survival Results in Major Switch Maintenance Trials in NSCLC

Switch Maintenance	Trial	PFS	OS
Docetaxel	Fidias et al[62]	5.7 months vs 2.7 months*	12.3 months vs 9.7 months
Erlotinib	SATURN[64]	12.3 weeks vs 11.1 weeks*	12 months vs 11 months*
Pemetrexed	JMEN[61]	4.3 months vs 2.6 months*	13.4 months vs 10.6 months

JMEN=Pemetrexed and Best Supportive Care Versus Placebo and Best Supportive Care in Non-Small Cell Lung Cancer; NSCLC=non–small cell lung cancer; OS=overall survival; PFS=progression-free survival; SATURN=Sequential Tarceva in Unresectable NSCLC.
*Statistically significant (P<.05).

T-cell activation, and proliferation by blocking cytotoxic T-lymphocyte associated antigen 4 (CTLA-4), a negative regulator of T-cells.[46] It is the first agent to show an overall survival benefit in metastatic melanoma.[47] Based on the success of ipilumumab in melanoma, trials in other tumor types, including NSCLC, are in progress. A recent phase II trial showed improved immune-related PFS (irPFS) when ipilumumab was combined with carboplatin and paclitaxel in first-line treatment of NSCLC.[48] Statistically significant improvement in irPFS was seen in the sequential arm (HR, 0.686; P=.025) when ipilumumab was added to chemotherapy after the second cycle and not in the concurrent arm. The potential benefit of sequential ipilumumab suggests that T-cell exposure to tumor antigens before ipilumumab administration may improve response.

Another immunotherapeutic agent with an interesting mechanism of action is talactoferrin. Talactoferrin is a recombinant form of human lactoferrin, and is identical to human lactoferrin, except in its glycosylation.[49] Interestingly, oral talactoferrin is not systemically absorbed.[50] In preclinical studies, following oral administration, talactoferrin is transported into intestinal Peyer's Patches (aggregated lymphoid nodules), where it recruits circulating dendritic cells,[51] inducing a strong, systemic, innate and adaptive immune response, which leads to immune-cell infiltration of distant tumors.[52] In a single-agent, phase II trial, oral talactoferrin extended OS in patients with refractory NSCLC by 2.3 months (P<.05, one-tailed log-rank test).[53,54] To confirm the phase II data, the trial known as FORTIS-M (A Phase 3, Randomized, Double-blind, Placebo-controlled Study of Oral Talactoferrin in Addition to Best Supportive Care in Patients With Non-small Cell Lung Cancer Who Have Failed Two or More Prior Treatment Regimens) has completed accrual.

Maintenance Therapy

Historically, the standard of care for first-line treatment of metastatic NSCLC has been a platinum doublet for 4–6 cycles, followed by observation until progression. New data with continuation or switch maintenance therapy are challenging that paradigm. The goal of continuation

maintenance is to give the same therapy past 4–6 cycles, with the hope that the additional administration of the same therapy will continue to suppress disease (Table 3). Switch maintenance changes therapy to a different second-line agent, with the hope of suppressing disease by delaying resistance to treatment (Table 4).

Continuation Maintenance

In all of the phase III trials of bevacizumab (Avastin, Genentech/Roche) in NSCLC, the anti-VEGF monoclonal antibody has been continued until progression or unacceptable toxicity, even after completion of 4–6 cycles of a platinum doublet. The AvaALL (MO22097) study is a randomized, phase IIIB trial that plans on continuing bevacizumab even after progression. The rationale for continuing bevacizumab beyond progression is based on a large observational cohort study in metastatic colorectal cancer, in which a significant OS benefit was seen in patients who received bevacizumab with chemotherapy beyond progression versus chemotherapy alone.[55] The reasons for this benefit are unclear, but this trial seeks to test the benefit of bevacizumab beyond progression in a prospective, randomized fashion in metastatic nonsquamous NSCLC.[56]

Regarding continuation maintenance for standard chemotherapy, both gemcitabine and pemetrexed have been studied, with mixed data for continuing gemcitabine. In 1 trial, continuing gemcitabine after response or disease stabilization with 4 cycles of cisplatin and gemcitabine showed increased TTP (6.6 months vs 5 months; 3.6 months vs 2 months for the maintenance period; $P<.001$) but no difference in OS (13 months vs 10 months).[57] Another phase III trial of gemcitabine as continuation maintenance after 4 cycles of carboplatin and gemcitabine failed to show a PFS or OS benefit in a phase III trial, but contained a high number of patients with poor performance status.[58]

The PARAMOUNT (Phase III Study of Maintenance Pemetrexed [pem] Plus Best Supportive Care [bsc] Versus Placebo Plus bsc Immediately Following Induction Treatment With Pem Plus Cisplatin for Advanced Nonsquamous Non-Small Cell Lung Cancer [NSCLC]) trial examined the benefit of continuing pemetrexed after 4 cycles of cisplatin and pemetrexed induction therapy in nonsquamous NSCLC patients. PFS from initiation of maintenance (4.1 months vs 2.8 months; $P<.0001$) and from start of induction therapy (6.9 months vs 5.59 months; $P<.0001$) was significantly improved.[59] Maintenance pemetrexed was generally well tolerated, and no difference was noted in health-related quality of life between the groups. The OS data have not yet been presented, but were included in the label for pemetrexed in Europe, and an OS benefit was demonstrated with pemetrexed maintenance. The study known as AVAPERL (A Study of Avastin [Bevacizumab] With or Without Pemetrexed as Maintenance Therapy After Avastin in First Line in Patients With Non-Squamous Non-Small Cell Lung Cancer) randomized responding or stable disease patients who received cisplatin, pemetrexed, and bevacizumab to either pemetrexed plus bevacizumab or bevacizumab alone. PFS in patients who received continuation maintenance with pemetrexed and bevacizumab was prolonged compared to bevacizumab alone (10.2 months vs 6.6 months; $P<.001$), and there was an OS benefit with the combination as well.[60] Similarly, the phase III Point-Break (JMHD) trial has completed accrual. This study randomized nonsquamous NSCLC patients to continuation maintenance with either bevacizumab alone or both pemetrexed and bevacizumab after 4 cycles of carboplatin, bevacizumab, and pemetrexed.

Switch Maintenance

Pemetrexed has also been studied in the switch-maintenance setting. Pemetrexed maintenance after 4 cycles of a nonpemetrexed, platinum-based doublet improves PFS (4.3 months vs 2.6 months; $P\leq.0001$) and OS (13.4 months vs 10.6 months; $P=.012$) compared with placebo.[61] Mainly adenocarcinoma histology patients benefited, and no OS benefit was seen in squamous histology patients. A criticism of the data is that 33% of patients randomized to placebo plus best supportive care did not go on to receive second-line treatment upon progression. A phase III Eastern Cooperative Oncology Group (ECOG) trial known as E5508 is ongoing. The trial is randomizing bevacizumab-eligible NSCLC patients to switch maintenance with either bevacizumab or pemetrexed monotherapy versus combined pemetrexed and bevacizumab after completing 4 cycles of carboplatin/paclitaxel/bevacizumab.

Docetaxel, gemcitabine, and erlotinib have also been studied in the switch maintenance setting. Immediate docetaxel compared to delayed docetaxel after frontline carboplatin and gemcitabine resulted in increased PFS of 3 months (5.7 months vs 2.7 months; $P=.0001$) and a trend towards increased OS (12.3 months vs 9.7 months; $P=.085$).[62] Quality of life scores were similar in both groups. A large portion in the delayed docetaxel group never received second-line therapy (37.2%) compared with the immediate docetaxel group (5.2%). The trend toward an OS benefit is explained by the inferior outcomes of patients who were not able to receive second-line docetaxel upon progression, as OS was nearly identical when comparing only patients who actually received docetaxel in both the immediate and delayed groups.

The benefit of erlotinib in relapsed/refractory disease was shown in the OS improvement in an unselected patient population seen in the BR21 trial that eventually led to the FDA approval of erlotinib in the third-line treatment setting.[63] The SATURN trial looked at erlotinib as maintenance therapy in unselected patients after completion of 4 cycles of platinum-based chemotherapy.[64] PFS (12.3 weeks vs 11.1 weeks; $P<.0001$) and OS (12 months vs 11 months; $P=.0088$) were prolonged in patients who received maintenance erlotinib. Although the benefit of erlotinib was most pronounced in patients who harbored EGFR-activating mutations, a subset analysis revealed a modest benefit in OS that extended to EGFR wild-type patients (HR, 0.77; confidence interval [CI], 0.61–0.97). In a subsequent preplanned analysis, the OS benefit in the SATURN trial was prolonged only in patients with stable disease after first-line chemotherapy (median OS, 11.9 months vs 9.6 months; HR, 0.72; $P=.0019$), and extended to patients whose tumors were EGFR wild-type.[65]

Conclusion

Targeted therapy has improved clinical outcomes for patients harboring EGFR activating mutations or ALK translocations. With the identification of substantial molecular heterogeneity in NSCLC, the clinical development of specific therapies against other molecular targets holds great promise. More progress has been made in lung adenocarcinoma histology, but new potential targets in squamous cell lung cancer have emerged. The keys to successful, targeted treatment are determining whether the targeted genetic alterations are driving tumor growth or are passive bystanders, and the continued development of therapies that specifically inhibit oncogene-addicted pathways. The development of new immunotherapies with intriguing mechanisms of action is also under way. Maintenance therapy has become a new treatment paradigm after first-line therapy, and is an appropriate option in selected patients.

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