Targeted Therapies for Lung Cancer

Thomas E. Stinchcombe

Abstract

Targeted therapies have become standard therapies for patients with non-small cell lung cancer (NSCLC). A phase III trial of carboplatin and paclitaxel with and without bevacizumab in patients with advanced NSCLC with non-squamous histology demonstrated a statistically significant improvement in efficacy. In patients with NSCLC with an activating epidermal growth factor receptor (*EGFR*) mutation (defined as exon 19 deletion and exon 21 L858R point mutation), phase III trials of EGFR tyrosine kinase inhibitors (TKI) compared to platinum-based chemotherapy have demonstrated superior efficacy in the first-line setting. In patients with NSCLC with anaplastic lymphoma kinase (*ALK*) rearrangements, phase III trials of crizotinib have demonstrated superior efficacy compared to platinum–pemetrexed in the first-line setting and standard chemotherapy in the second-line setting. A second-generation ALK inhibitor, ceritinib, is available for patients who have progressed after or were intolerant of crizotinib. Crizotinib has also demonstrated activity on patients with ROS1 rearrangements, and BRAF inhibitors (dabrafenib, vemurafenib) have demonstrated activity in patients with NSCLC with *BRAF* V600E mutation. The oncogenic mutations that are susceptible to targeted therapy are mainly found in non-squamous NSCLC. The development of targeted therapy in patients with squamous NSCLC has been more challenging due to the genomic complexity observed in the squamous histology and the low prevalence of *EGFR*, *ALK*, and *ROS1* molecular alterations. A phase III trial of cisplatin and gemcitabine with and without necitumumab in patients with advanced NSCLC with squamous histology demonstrated a statistically significant improvement in progression-free and overall survival.

T.E. Stinchcombe (✉)
University of North Carolina at Chapel Hill, 170 Manning Drive,
Physician's Office Building, 3rd Floor, Chapel Hill, NC 27599-7305, USA
e-mail: Thomas_stinchcombe@med.unc.edu

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Contents

1 Introduction

Lung cancer remains a leading cause of cancer-related mortality in the United States and globally [1–3]. The majority of patients have the non-small cell lung cancer (NSCLC) subtype and present with advanced stage disease at the time of diagnosis [4]. In patients with advanced NSCLC, defined as stage IIIB or IV disease, platinum-based chemotherapy was the mainstay of systemic therapy for several decades. However, clinical trials of various combinations of platinum doublets revealed a therapeutic plateau had been reached [5, 6]. Consequently, the focus of drug development became agents that targeted a critical cell signaling pathway or a specific oncogenic process. Several targeted agents have become standard of care in the treatment of NSCLC, and others are currently in development. The identification and development of predictive biomarkers for targeted therapies have accelerated the pace of drug development and significantly improved the clinical care of patients with advanced NSCLC. The currently available targeted therapies are most frequently used in patients with NSCLC with non-squamous histology. The development of targeted therapies for small cell lung cancer (SCLC) and NSCLC with squamous histology has been more challenging.

2 Anti-angiogenesis Agents

The ability to develop new blood vessels is one the hallmarks of cancer and new blood vessels provide oxygen and nutrients to sustain tumor growth and can provide a conduit for development of new metastatic lesions [7]. Disrupting the process of angiogenesis was a focus of extensive research. The first anti-angiogenesis agent available for advanced NSCLC was bevacizumab, a monoclonal antibody that target vascular endothelial growth factor (VEGF) A, which is a ligand that binds to VEGF receptors. A randomized phase II trial investigated carboplatin and paclitaxel alone and with bevacizumab at 7.5 mg/kg every three weeks or 15 mg/kg every three weeks in advanced NSCLC (all histologies) [8]. This trial established the bevacizumab dose of 15 mg/kg every three weeks as the preferred dose for further investigation in combination with carboplatin and paclitaxel. A prohibitive rate of pulmonary hemorrhage was observed in patients with squamous histology treated with bevacizumab, and patients with squamous histology were excluded from subsequent trials. The phase III trial compared carboplatin and paclitaxel with and without bevacizumab in patients with advanced NSCLC with non-squamous histology. Patients with hemoptysis, uncontrolled hypertension, clinically significant cardiovascular disease, and on therapeutic anticoagulation were excluded. This trial revealed a statistically superior objective response rate (ORR), progression-free survival (PFS), and overall survival (OS) with the addition of bevacizumab (Table 1) [9]. A three arm phase III trial investigated cisplatin and gemcitabine with placebo, bevacizumab 7.5 mg/kg every three weeks, or 15 mg/kg every three weeks in patients with advanced NSCLC with non-squamous histology (Table 1) [10, 11]. The primary end-point was PFS, and the trial was not designed to compare the efficacy of the two bevacizumab arms. Patients assigned to bevacizumab 7.5 mg/kg or 15 mg/kg every three weeks arms compared to the placebo arm had a statistically superior ORR and PFS; a statistically significant difference in the secondary end-point of OS was not observed between the individual bevacizumab arms compared to placebo. The unique grade 3 or 4 bevacizumab-related toxicities observed in these trials were hypertension, proteinuria, and hemorrhage (pulmonary or gastrointestinal). Bevacizumab in combination with platinum-based therapy was the first targeted therapy, demonstrating an improvement in outcome compared to platinum-based chemotherapy alone. However, concerns about toxicities, treatment restrictions related to the comorbidities, and the lack of a predictive biomarker have limited the future development of the agent.

Ramucirumab is a monoclonal antibody against the extracellular domain of VEGF receptor 2, and a phase III trial investigated docetaxel with placebo or ramucirumab in patients who had experienced disease progression after platinum-based therapy [12]. There were no eligibility restrictions related to histology, and approximately 25 % of the patients enrolled had squamous NSCLC. A statistically significant higher ORR, longer PFS, and longer OS were observed in patients assigned to the ramucirumab compared to the placebo arm (Table 1).

Table 1 Select phase III trials of anti-angiogenesis agents in advanced non-small cell lung cancer

Comparison (# of patients)	Line of therapy	Objective response rate	Median progression-free survival	Median overall survival
Carboplatin and paclitaxel ± bevacizumab [9] (n = 838)	First-line	35 % versus 15 % $p < 0.001$	6.2 versus 4.5 months HR = 0.66, $p < 0.001$	12.3 versus 10.3 months HR = 0.79, $p = 0.003$
Cisplatin/gemcitabine with placebo [10, 11] bevacizumab 7.5 mg/kg bevacizumab 15 mg/kg (n = 1043)[a]	First-line	20.1 % 34.1 % ($p < 0.0001$) 30.4 % ($p = 0.0023$)	6.1 months 6.7 months, HR = 0.75, $p = 0.003$ 6.5 months, HR = 0.82, $p = 0.03$	13.1 months 13.6 months, HR = 0.93, $p = 0.420$ 13.4 months, HR = 1.03, $p = 0.761$
Docetaxel with placebo or ramucirumab [12] (n = 1253)	Second-line	23 % versus 14 % $P < 0.0001$	4.5 versus 3.0 months HR = 0.76, $p < 0.0001$	10.5 versus 9.1 months HR = 0.86, $p = 0.023$

[a]This is a 3-arm trials and bevacizumab 7.5 mg/kg and 15 mg/kg were compared to placebo arm
HR: hazard ratio

A higher rate of toxicity was not observed in the squamous histology subset. In the ramucirumab compared to the docetaxel alone arm, a higher rate of febrile neutropenia was observed (10 % vs. 6 %); a similar rate of grade ≥3 hemorrhage (2 % in each arm) and hypertension (6 % vs. 2 %) were observed in the two arms. A predictive biomarker for ramucirumab has not been identified.

3 Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase Inhibitors in EGFR Mutant NSCLC

In the early trials of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI), patients with history of light or never smoking, adenocarcinoma histology, and Asian ethnicity were observed to higher response rate [13]. Patients with these clinical characteristics were subsequently found to have a high rate of activating *EGFR* mutations, defined as exon 19 deletions or exon 21 L858R point mutations [14, 15]. Based on these clinical observations, a prospective phase III trial compared gefitinib to carboplatin/paclitaxel in patients with a history of light or never smoking and advanced NSCLC with adenocarcinoma histology was performed in Asia [16]. Patients assigned to the gefitinib compared to carboplatin and paclitaxel arm experienced a statistically significant higher ORR and longer PFS in the intent-to-treat patient population. In the subgroup of patients with a confirmed EGFR mutation (n = 261), patients assigned to gefitinib compared to carboplatin and paclitaxel experienced a statistically significant higher ORR and PFS (Table 2). Patients who did not have an *EGFR* mutation (n = 176) assigned to the gefitinib

arm compared to the carboplatin and paclitaxel arm had a statistically significant lower ORR (1.1 % vs. 23.5 %, $p < 0.001$) and shorter PFS (HR of 2.85; 95 % CI, 2.05–3.98, $p < 0.001$; median PFS of 1.5 and 5.5 months) [16, 17]. The rate of *EGFR* mutations in this clinically enriched cohort was approximately 60 %. This trial established *EGFR* mutation as opposed to *EGFR* fluorescence in situ hybridization (FISH) and EGFR immunohistochemistry (IHC) as the preferred biomarker for selection of EGFR TKI therapy [17]. It also established that clinical characteristics were not sufficient to select patients for first-line EGFR TKI and *EGFR* mutation testing was required. Additional trials comparing EGFR TKI to platinum doublets have been performed which required the presence of an *EGFR* mutation for enrollment (Table 2). These trials have consistently shown a

Table 2 Select trials of epidermal growth factor receptor tyrosine kinase inhibitors compared to platinum-based chemotherapy

Trial (# of patients)	Comparison	Objective response rate	Median progression-free survival	Median overall survival
IPASS [16, 17] ($n = 261$)[a]	Gefitinib versus carboplatin and paclitaxel	71.2 % versus 47.3 % $p < 0.001$	9.5 versus 6.3 months HR = 0.48, $p < 0.001$	21.6 versus 21.9 HR = 1.00, $p = 0.990$
NEJSG [18] ($n = 200$)	Gefitinib versus carboplatin and paclitaxel	73.7 % versus 30.7 % $P < 0.001$	10.8 versus 5.4 months HR = 0.30, $p < 0.001$	30.5 versus 23.6 months $P = 0.31$
WJTOG [19] ($n = 172$)	Gefitinib versus cisplatin and docetaxel	62.1 % versus 32.2 % $P < 0.0001$	9.2 versus 6.3 months HR = 0.489, $p < 0.0001$	30.9 versus not reached HR = 1.638, $p = 0.211$
CTONG [24] ($n = 165$)	Erlotinib versus carboplatin and gemcitabine	83.0 % versus 36 % $P < 0.0001$	13.1 versus 4.6 months HR = 0.16, $p < 0.001$	22.69 versus 28.85 months HR = 1.04, $p = 06915$
EURTAC [23] ($n = 174$)	Erlotinib versus platinum-doublet	58 % versus 15 %	9.7 versus 5.2 months HR = 0.37, $p < 0.0001$	19.3 versus 19.5 months HR = 1.04, $p = 0.87$
LUX Lung-3 [21] ($n = 345$)	Afatinib versus cisplatin and pemetrexed	56 % versus 23 % $P < 0.001$	11.1 versus 6.9 months HR = 0.58, $p < 0.001$	28.2 versus 28.2 months HR = 0.88, $p = 0.39$
LUX Lung-6 [20] ($n = 364$)	Afatinib versus cisplatin and gemcitabine	66.9 % versus 23.0 % $P < 0.0001$	11.0 versus 5.6 months HR = 0.28, $p < 0.0001$	23.1 versus 23.5 months HR = 0.93, $p = 0.61$

IPASS Iressa Pan Asia Study, *NEJSG* North East Japan Study Group, *WJTOG* West Japan Thoracic Oncology Group, *CTONG* Chinese Thoracic Oncology Group, *EURTAC* European Tarceva versus Chemotherapy, *HR* hazard ratio

[a]The data represent the subgroup with a confirmed *EGFR* mutation

superiority in ORR, PFS, and quality of life in the EGFR TKI arm [18–26]. The most common adverse events observed with this class of agents are rash and diarrhea, and less common serious adverse events include stomatitis, paronychia, and interstitial pneumonitis.

Retrospective analyses observed that patients with *EGFR* exon 19 deletions compared to exon 21 L858R had better outcomes with EGFR TKIs, but clinically patients with exon 19 or 21 *EGFR* mutations were treated the same. A recent combined analysis of two trials of afatinib compared to platinum-based chemotherapy has challenged the assumption *EGFR* exon 19 and exon 21 should be treated similarly [27]. In the combined analysis of the two trials, in patients with an *EGFR* exon 19 and exon 21 L858R mutations ($n = 631$) a statistically significant longer OS was observed in patients assigned to afatinib compared to platinum-based therapy (hazard ratio (HR) of 0.81, 95 % confidence interval (CI), 0.66–0.99; $p = 0.037$; median OS of 27.3 and 24.3 months, respectively). When patients were analyzed by mutation type, the OS difference remained statistically significant in the exon 19 deletion patient subgroup ($n = 355$, HR of 0.59, 95 % CI, 0.45–0.77; $p = 0.0001$; median OS of 31.7 and 20.7 months, respectively). However, a statistically significant difference in OS was not observed in the exon 21 L858R deletion subgroup ($n = 276$, HR of 1.25, 95 % CI, 0.92–1.71; $p = 0.16$; median OS of 22.1 and 26.9 months, respectively). This observation raises the question whether afatinib is a better EGFR TKI for patients with *EGFR* exon 19 deletions since previous trials of EGFR TKI compared to platinum-based therapy have revealed an improvement in ORR and PFS, but not an OS improvement in the intent-to-treat patient population.

The development of EGFR TKI therapy in patients with *EGFR* mutant NSCLC has been a significant therapeutic advance; however, disease progression is inevitable and generally occurs within 10–15 months. Multiple mechanisms of resistance have been identified, but approximately 50–60 % of *EGFR* mutant NSCLC develop a T790M resistance mutation [28–30]. A separate chapter focuses of the mechanisms of resistance and drugs in development for this patient population.

4 EGFR Tyrosine Kinase Inhibitors in Second- or Third-Line Setting

Erlotinib is currently available for patients who have progressed on platinum-based chemotherapy based on a phase III trial of erlotinib compared to best supportive care which revealed an improvement in ORR, PFS, OS, and QoL [31, 32]. An analysis of the benefit according to tumor molecular characteristics revealed that OS was not influenced by *EGFR* mutation status [33]. Thus, erlotinib is available as a treatment in the second- and third-line settings regardless of *EGFR* mutation status. However, the limited activity observed in the *EGFR* wild-type NSCLC in the first-line setting raised questions about the efficacy of EGFR TKIs in the second- and third-line settings. A prospective trial enrolled patients who had experienced disease progression after platinum-based therapy with *EGFR* wild-type tumors to

docetaxel or erlotinib (n = 222) [34]. Patients assigned to the docetaxel compared to erlotinib experienced a superior OS (HR of 0.73, 95 % CI, 0.523–1.00; p = 0.05; median OS of 8.2 and 5.4 months, respectively) and PFS (HR of 0.71, 95 % CI, 0.53–0.95; p = 0.02; median 2.9 and 2.4 months). These data support the use of chemotherapy as the preferred second-line therapy for patients who are candidates for second-line chemotherapy.

There has been considerable interest in defining an *EGFR* mutation wild-type patient population who may benefit from EGFR TKIs in the second- and third-line setting based on clinical factors or a predictive biomarker. A multivariate serum proteomic test can classify patients into two categories related to good or poor outcome from EGFR TKI therapy [35]. A phase III trial prospectively assessed the proteomic signature and stratified patients based on good or poor status and then randomized patients to erlotinib or second-line chemotherapy [36]. A statistically significant interaction between treatment and proteomic classification was observed (p = 0.017). Among patient with proteomic classification of good, patients assigned to the chemotherapy compared to erlotinib had a similar OS (HR of 1.06, 95 % CI, 0.77–1.47; p = 0.714; median OS of 10.9 and 11.0 months). Among patients with proteomic classification of poor, patients assigned to the erlotinib arm compared to the chemotherapy arm had a statistically significant worse OS (HR of 1.72, 95 % CI, 1.08–2.74, p = 0.022; median of OS of 3.0 and 6.4 months). Patients with the serum proteomic status of poor should not receive erlotinib, and the primary utility of the test is in *EGFR* wild-type NSCLC.

5 Adjuvant Epidermal Growth Factor Tyrosine Kinase Inhibitors

Given the promising activity of EGFR TKIs in patients with metastatic *EGFR* mutant NSCLC, there is significant interest in developing the agents as adjuvant therapy for patients with completely resected *EGFR* mutant NSCLC. A single-arm phase II trial investigated erlotinib 150 mg daily for two years in patients with resected stage IA to IIIA *EGFR* mutant NSCLC [37]. The primary end-point was 2-year disease-free survival (DFS) of 86 %, and a 100 patients were enrolled. Of the patients enrolled, 69 % of patients tolerated at least 22 months of erlotinib, and 40 % need at least one dose reduction. The 2-year DFS observed was 89 %, and median DFS has not yet been reached. Twenty-nine patients have recurred, and the median time recurrence after stopping erlotinib was 8.5 months (range 0–47 months). The OS data is immature.

A phase III trial investigated adjuvant erlotinib compared to placebo in patients with resected stage IB to IIIA NSCLC with EGFR-positive IHC or FISH. Patients could have received adjuvant chemotherapy. The primary end-point was DFS, and the patients assigned to adjuvant erlotinib compared to placebo experienced a similar DFS in the intent-to-treat patient population (HR of 0.90; 95 % CI, 0.741–1.104; p = 0.3235; median DFS 50.2 and 48.2 months, respectively). Of the 973

patients enrolled, 161 patients had NSCLC harboring an *EGFR* mutation. Patients with *EGFR* mutant NSCLC assigned to the erlotinib compared to the placebo arm had a longer DFS (HR of 0.61, 95 % CI, 0.384–0.981; $p = 0.0391$). Due to the hierarchical testing procedure, this result is not considered statistically significant.

At this time, the data do not support the use of adjuvant EGFR TKI in unselected patients. In *EGFR* mutant NSCLC, adjuvant EGFR TKI appears to delay disease recurrence, but data demonstrating improvement in OS are not available. There remain several significant concerns about the use of adjuvant EGFR TKI including the potential to development of acquired resistance to EGFR TKIs, and the questions about the appropriate dose and duration of therapy. The National Cancer Institute Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial (ALCHEMIST, NCT02194738) is currently screening surgically resected patients for molecular abnormalities [38]. Patients with *EGFR* mutant NSCLC will be enrolled on a clinical trial ALCHEMIST-EGFR (NCT02193282) which investigates adjuvant erlotinib 150 mg daily for two years compared to placebo. The primary end-point is OS, and the trial will enroll 410 patients. At this time, the use adjuvant EGFR TKI cannot be recommended outside the context of a clinical trial, and patients should be encouraged to enroll in the ALCHEMIST trial.

6 Anaplastic Lymphoma Kinase Inhibitors

Anaplastic lymphoma kinase (*ALK*) rearrangements were first detected in NSCLC in 2007, and the rate of *ALK* translocations among patients with adenocarcinoma is estimated to be approximately 8 % [3]. *ALK* rearrangements are more common in patients with adenocarcinoma histology and a history of never or light smoking [39, 40]. The anaplastic lymphoma kinase inhibitor crizotinib was approved in 2011 based on the promising activity observed in a phase I study with an expansion cohort in patients with advanced NSCLC and a confirm *ALK* rearrangement [41]. The early identification of a predictive biomarker significantly accelerated the drug development and approval process of crizotinib. Two subsequent trials investigated crizotinib in patients with advanced NSCLC with a confirmed *ALK* rearrangement compared to platinum–pemetrexed in first-line setting or compared to docetaxel or pemetrexed in the second-line setting [42, 43]. In both trials, patients assigned to crizotinib compared to chemotherapy had a statistically significant higher ORR and longer PFS, and better QoL (Table 3). Patients with *ALK* rearrangement appear to have a higher ORR with pemetrexed compared to historical controls of unselected patients with non-squamous histology who received pemetrexed [43, 44]. The most common adverse events observed with crizotinib are visual disturbances, diarrhea, edema, vomiting, constipation, and elevated liver enzymes. The most common grade 3 or 4 adverse events occurring at a rate of >5 % are elevated liver enzymes and neutropenia.

Ceritinib is a second-generation ALK inhibitor that is 20 times as potent ALK inhibitor as crizotinib. Ceritinib has revealed activity in patients who have progressed after crizotinib or who were intolerant of crizotinib and crizotinib-naïve

Table 3 Select trials of ALK inhibitors in patients with NSCLC with ALK rearrangements

Comparison (# of patients)	Objective response rate	Median progression-free survival	Median overall survival
Crizotinib versus chemotherapy (docetaxel or pemetrexed) (n = 347) [43]	65 % versus 20 % $p < 0.001$	7.7 versus 3.0 months HR = 0.49, $p < 0.001$	20.3 versus 22.8 months HR = 1.02, $p = 054$
Crizotinib versus platinum–pemetrexed (n = 343) [42]	74 % versus 45 % $P < 0.001$	10.9 versus 7.0 months HR = 0.45, $p < 0.001$	Not reached HR = 0.82, $p = 0.36$
Ceritnib [45] (n = 114) Ceritinib (prior crizotinib) (n = 80) Ceritinib (crizotinib naïve) (n = 34)	58 % 56 % 62 %	7.0 months 6.9 months Not reached	Not reached Not reached Not reached
Alectinib (prior crizotinib) [47] (n = 47) Alectinib (crizotinib naïve) [46] (n = 43)	55 % 93.5 %	Not reached Not reached	Not reached Not reached

ALK anaplastic lymphoma kinase, *HR* hazard ratio
[a]Data represent patients receiving a minimum of ceritinib 400 mg daily

patients (Table 3) [45]. The grade 3 or 4 adverse events occurring at a rate of >5 % are elevated liver enzymes, diarrhea, elevated lipase, nausea, fatigue, and vomiting. Approximately 60 % of patients treated at the approved dose of 750 mg required at least one dose reduction. Responses were observed in patients with untreated CNS lesions which is clinically relevant since many patients are presented with or develop brain metastases.

Alectinib is a highly selective ALK inhibitor that has demonstrated activity against the L1196M crizotinib resistance mutation [46]. Alectinib was investigated in phase I/II trial in patients with *ALK* rearranged NSCLC who ALK inhibitor naïve; the primary end-point of the phase II was ORR. The recommended dose for phase II was 300 mg twice daily, and the ORR observed in the phase II cohort was 93.5 % (95 % CI, 82.1–98.6 %). The grade 3 treatment-related adverse events observed were decreased neutrophil count (4 %), increased creatinine phosphokinase (4 %), increased liver enzymes (2 %), increased bilirubin (2 %), and rash (2 %). The data on PFS was immature at the time publication. Activity was demonstrated in patients with treated and untreated brain metastases. Alectinib was investigated in a separate phase I/II trial in patients with *ALK* rearranged NSCLC who had progressed on or were intolerant of crizotinib; the primary end-point of the phase II trial was ORR [47]. Alectinib 600 mg twice a day was selected based on the toxicities and tolerability observed in the phase I portion of the trial for further investigation in the phase II portion of the trial. The ORR observed was 55 %, and the PFS data were immature at the time of publication. Of the 21 patients with CNS

disease at baseline, 52 % had an objective response and 38 % had stable disease. The most common grade 3 or 4 adverse events were increased gamma-glutamyl transpeptidase, decreased neutrophil count, and hypophosphatemia. Both alectinib and ceretinib have demonstrated activity in patients who have progressed on or were intolerant of crizotinib, in patients with CNS disease, and ALK inhibitor-naïve patients.

ROS1 rearrangements are detected in approximately 1 % of cases of NSCLC and are more commonly found in patients with a history of never or light smoking and adenocarcinoma histology [48]. Preclinical data revealed significant activity of crizotinib in cell lines with *ROS1* rearrangements [48]. A single-arm phase II trial investigated crizotinib in 50 patients who tested for *ROS1* rearrangement revealed an ORR of 72 % (95 % CI, 58–84 %), and a median PFS of 19.2 months (95 % CI, 14.4 to not reached) [49]. A second study of 30 patients revealed an ORR of 80 % and a median PFS of 9.1 months [50]. Both of these trials are small, but demonstrate significant activity of crizotinib in patients NSCLC with *ROS1* rearrangements.

7 BRAF Inhibitors

BRAF mutations are detected in approximately 2–3 % of NSCLC with adenocarcinoma histology and are more frequently detected in patients with a history of tobacco use, and approximately 50–75 % of the *BRAF* mutations are the *BRAF* V600E mutation seen in melanoma [3, 51]. Vemurafenib and dabrafenib have demonstrated significant activity in patients with metastatic melanoma who harbor a *BRAF* V600E mutation. A single-arm phase II trial investigated dabrafenib in patients with advanced stage NSCLC with *BRAF* V600E mutant NSCLC (n = 84). The ORR by independent review committee was 28 % (95 % CI, 18–41 %) [52]. Given the activity of the BRAF inhibitors in combination with MEK inhibitors observed in BRAF V600E mutant melanoma, the combination of dabrafenib and trametinib was investigated in a single-arm phase II trial in patients with *BRAF* V600E mutant NSCLC (n = 33) [53]. An interim analysis revealed an ORR of 63 % (95 % CI, 40.6–81.2 %), and the trial meet the criteria to continue to the second stage. Grade 3 adverse events occurred in 39 % of patients, and the most frequent grade 3 adverse events were hyponatremia (6 %), neutropenia (6 %), and dehydration (6 %). One patient had grade 4 hyponatremia and one patient had grade 5 pleural effusion. Case reports have demonstrated activity of vemurafenib in patients with *BRAF* mutant V600E NSCLC [54, 55]. While these data are not definitive, they do suggest potential activity of BRAF inhibitors alone and in combination with MEK inhibitors in patients with NSCLC with a *BRAF* V600E mutation.

8 Squamous NSCLC

The development of targeted therapies for NSCLC with squamous histology has been more difficult, and this subtype of NSCLC has a lower rate of *EGFR* mutations and *ALK* rearrangements. A retrospective found the rate of EGFR mutations in patients with squamous histology based on immunohistochemistry testing was 0 % (95 % CI, 0–3.8 %) [56]. Given the low prevalence of *EGFR* mutations and *ALK* rearrangements, routine molecular testing is not recommended. NSCLC with squamous histology also have greater genomic complexity and frequently a single tumor will have multiple oncogenic mutations which makes it less susceptible to an agent that inhibits a single oncogenic pathway [57].

A phase III trial investigated cisplatin and gemcitabine with and without necitumumab, a monoclonal antibody against the extracellular domain of the EGFR receptor, in patients with advanced NSCLC with squamous histology [58]. Patients assigned to the necitumumab containing arm compared to the chemotherapy alone arm experienced a similar response rate (31.2 % vs. 28.8 %, $p = 0.400$), but a statistically significant longer PFS (HR of 0.85; 95 % CI, 074–098; $p = 0.20$; median 5.7 and 5.5 months, respectively) and OS (HR of 0.84, 95 % CI, 074–0.96; $p = 0.012$; median OS of 11.5 and 9.9 months). Patients assigned to the necitumumab compared to the chemotherapy alone arm experienced a higher rate of grade ≥3 hypomagnesemia (9.3 % vs. 1.1 %), and skin rash (7.1 % vs. 0.4 %). An exploratory analysis of EGFR expression using the H-score found that the H-score was not predictive of PFS or OS benefit with necitumumab. While the OS benefit is modest, this trial does represent the first improvement in OS with a targeted therapy in combination with platinum-based chemotherapy compared to platinum-based chemotherapy alone in patients with squamous NSCLC.

A phase III study investigated afatinib compared to erlotinib as second-line therapy in patients with squamous histology who had experienced disease progression after platinum-based therapy ($n = 795$) [59]. The primary end-point was PFS, and a secondary end-point was OS. Patients assigned to afatinib compared to erlotinib experienced a statistically significant longer PFS (HR of 0.81, 95 % CI, 0.69–0.96; $p = 0.01$; median PFS of 2.6 and 1.9 months, respectively) and OS (HR of 0.81, 95 % CI, 0.69–0.95; $p = 0.008$; median OS of 7.9 and 6.8 months, respectively). Patients assigned to the afatinib compared to the erlotinib arm experienced a higher rate of treatment-related grade 3 or 4 diarrhea (10.4 % vs. 2.6 %), grade 3 stomatitis (4.1 % vs. 0 %), and a lower rate of grade 3 rash (5.9 % vs. 10.4 %). Patients assigned to afatinib compared to erlotinib experienced a statistically significant improvement in global quality of life and improvement in the symptoms of cough and dyspnea. Afatinib is currently available for first-line therapy for patients with NSCLC with *EGFR* exon 19 and 21 mutations and as second-line therapy for patients with metastatic squamous NSCLC.

9 Small Cell Lung Cancer

Small cell lung cancer (SCLC) frequently demonstrates multiple oncogenic mutations and has inactivation of the tumor suppressor genes *p53* and *RB1*, and to date, a mutation that is susceptible to tyrosine kinase inhibitor has not been identified [60, 61]. Anti-angiogenesis therapy has been investigated in extensive stage (ES-SCLC), and agents have been shown to extend PFS but not OS. A randomized phase II investigate platinum etoposide with and without bevacizumab, and the primary end-point was PFS (n = 102) [62]. Patients assigned to the bevacizumab arm experienced a statistically significant longer PFS (HR of 0.53; 95 % CI, 0.32–0.86; median 5.5 and 4.40 months, respectively) and similar OS (HR of 1.16; 95 % CI, 0.66–2.04; median 9.4 and 10.9 months, respectively). A randomized phase II trial investigated maintenance sunitinib compared to placebo in patients who had stable disease or response to four or six cycles of platinum–etoposide [63]. Of the 138 patients who initiated chemotherapy, 85 patients were randomized to sunitinib or placebo. Patients assigned to placebo compared to sunitinib had a statistically significant worse PFS (HR of 1.62; 95 % CI, 1.02–2.60; p = 0.02; median PFS 2.1 and 3.7 months, respectively) and similar OS (HR of 1.28; 95 % CI, 0.79–2.10; p = 0.16; median OS of 6.9 and 9.0 months, respectively). While both of these trials met the primary end-point of improvement in PFS, it is unlikely that either of these agents will be investigated in a phase III trial.

10 Conclusions

There are currently several standard targeted therapies available for patients with advanced NSCLC, and the targeted therapies generally fall into two classes: monoclonal antibodies against a specific target or tyrosine kinase inhibitors. In general, the monoclonal antibodies have demonstrated modest differences in efficacy and do not have a biomarker to select patients for treatment. TKIs have demonstrated significant efficacy, and several predictive molecular markers are available (e.g., *EGFR* mutation status, and *ALK* or *ROS1* rearrangements). The development of predictive biomarker for targeted therapies has significantly accelerated drug development and improved clinical care in a relatively short period of time. Targeted therapies are the focus of drug development in lung cancer, and a number of promising agents are in development. The development of widely available next-generation tumor sequencing has made the identification of patients for targeted therapies much convenient and efficient.

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