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Recent advances in the treatment of non-small cell and small cell lung cancer

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Abstract

Recent presentations at the American Society of Clinical Oncology (ASCO) meeting from 30 May to 3 June, 2014, will impact routine clinical care and the development of clinical trials in non-small cell lung cancer (NSCLC) and extensive stage small cell lung cancer (ES-SCLC). Patients with activating epidermal growth factor receptor (*EGFR*) mutations, defined as exon 19 and exon 21 L858R point mutations, experience a high objective response rate and prolonged progression-free survival with EGFR tyrosine kinase inhibitors. However, inevitably, patients experience disease progression and the most common mechanism of acquired resistance is an *EGFR* exon 20 T790M mutation. Several agents (AZD9291, CO-1686 and HM61713) have demonstrated impressive activity in patients with T790M resistance mutations. Additional data on the efficacy of first-line therapy with afatinib and the combination of erlotinib and bevacizumab for patients with *EGFR* mutant NSCLC were presented. The results of a phase III trial of crizotinib compared to platinum-pemetrexed in the first-line setting, and a phase I trial and expansion cohort of ceritinib, provided additional efficacy and toxicity data for patients with anaplastic lymphoma kinase rearranged NSCLC. A phase III trial of cisplatin and gemcitabine, with and without necitumumab, revealed an improvement in overall survival with the addition of necitumumab in patients with squamous NSCLC. In the second-line setting, a phase III trial of docetaxel with ramucirumab or placebo revealed an improvement in overall survival with the addition of ramucirumab. In extensive stage small cell lung cancer phase III trials of consolidative thoracic radiation therapy and prophylactic cranial radiation failed to reveal an improvement in overall survival.

Introduction

The recent presentations at ASCO revealed significant progress in the treatment of NSCLC, and the ever increasing role of targeted therapies in molecularly defined sub-types for NSCLC. Novel agents revealed activity in the epidermal growth factor receptor (*EGFR)* mutant positive NSCLC, and anaplastic lymphoma kinase (*ALK*) rearranged NSCLC. Other trials reported the results of EGFR tyrosine kinase inhibitors alone and in combination with bevacizumab in the first-line metastatic setting, and EGFR tyrosine kinase inhibitor therapy in the adjuvant setting. A phase III trial of cisplatin and gemcitabine with and without necitumumab, a monoclonal antibody against the extracellular domain of EGFR, revealed a statistically significant improvement in overall survival in patients with advanced NSCLC with squamous histology. A phase III trial of docetaxel with and without ramucirumab—a monoclonal antibody against vascular endothelial growth factor receptor 2 (VEGFR-2)—in unselected patients in the second-line setting demonstrated an improvement in overall survival. Trials investigated the role of thoracic radiotherapy and prophylactic cranial irradiation in the treatment of ES-SCLC, but these two commonly used practices did not reveal an improvement in overall survival. This review will focus on the presentations that are most likely to impact clinical care and trials in the next several years.

Recent advances in treatment

Novel "third generation" EGFR tyrosine kinase inhibitors

Most patients with *EGFR* mutant NSCLC receive an EGFR tyrosine kinase inhibitor (e.g. gefitinib, erlotinib, or afatinib) as first-line therapy, and unfortunately most patients experience disease progression after approximately 10–15 months of treatment. The most common mechanism of resistance is an *EGFR* exon 20 T790M mutation, which is detected in approximately 50–60% of tumor samples when a biopsy is performed after disease progression on EGFR tyrosine kinase inhibitors [1,2]. Preclinical models revealed that covalent pyrimidine EGFR inhibitors (compared to the quinazoline-based EGFR inhibitors) were 30- to 100-fold more potent against the EGFR T790M, and up to 100-fold less potent against EGFR wild-type [3]. These agents demonstrated activity of lung cancer driven by the EGFR T790M in murine models [3]. These preclinical data led to the development of several novel EGFR tyrosine kinase inhibitors in order to combat acquired resistance to EGFR tyrosine kinase inhibitors (AZD 9291, CO-1686, and HM61713). While it is tempting to compare and contrast these agents, there are insufficient data at this time to make accurate conclusions. In general, all these agents have greater activity in T790M positive than in T790M negative *EGFR* mutant NSCLC, have a lower rate of EGFR wild-type associated toxicities of rash and diarrhea than currently available EGFR tyrosine kinase inhibitors, and have demonstrated activity even at low doses.

AZD9291 is an oral mutant selective EGFR tyrosine kinase inhibitor that was investigated in a phase I trial in patients with documented radiological progression after prior EGFR tyrosine kinase inhibitor therapy using a rolling six design [4]. Patients were not selected based on T790M status in the dose escalation phase, but enrollment in the expansion cohorts required central laboratory testing confirmation of the T790M mutation. Thirty-one patients were enrolled in the dose escalation and 201 patients in the expansion cohorts. The maximum tolerated dose (MTD) has not been defined and no dose-limiting toxicities (DLTs) were observed. Based on the toxicities and activity observed, the recommended dose for phase II trials is 80 mg oral daily. In the 80 mg dose cohort (n = 74) the rate of any grade and grade ≥3 rash was 27% and 0% of patients, respectively, and the rate of any grade and grade ≥3 diarrhea was 20% and 1% of patients, respectively. In the 80 mg cohort, 1% of patients experienced any grade hyperglycemia and QT prolongation and any grade and grade ≥3 interstitial lung disease was observed in 3% and 1% of patients, respectively. The objective response rate (ORR) observed in the study population (n = 205) was 53% (95% confidence interval [CI], 46 to 60%), and was similar in all dose cohorts. The ORR in patients with centrally confirmed T790M mutation (n=107) was 64% (95% CI, 55 to 73%) and in patients without evidence of T790M mutation (n = 50) was 22% (95% CI, 12 to 36%). The progression-free survival rate was numerically longer in the patients with T790M mutation.

CO-1686 was investigated in a phase I/II study in patients with activating *EGFR* mutation, prior treatment with EGFR-directed therapy, and a T790M mutation at the time of study entry [5]. In the phase II dose expansion cohorts, patients were defined as second-line patients with progressive disease on EGFR tyrosine kinase inhibitors immediately prior to study entry, and progressive disease in second-line clinical setting with progressive disease on EGFR tyrosine kinase inhibitors or chemotherapy. The adverse events observed (n = 72) include rash in 4% of patients (all grade 1) and all grade and grade 3 diarrhea in 23% and 0% of patients, respectively. Other notable adverse events were all grade and grade 3 hyperglycemia in 53% and 22% of patients, respectively (which was managed with metformin), and all grade and grade 3 QT prolongation in 15% and 7% of patients, respectively. The ORR in patients with centrally confirmed T790M mutation (n = 40) was 58%, and the median progression-free survival was not reached but is estimated to be >12 months.

A phase I trial investigated HM61713 in patients with an EGFR mutation, and a dose expansion cohort at 300 mg daily; in the dose expansion cohort patients were classified as experiencing disease progression on EGFR tyrosine kinase inhibitors within or greater than 4 weeks [6]. The MTD has not been reached and two DLTs were observed (1 patient with grade 3 rash, and 1 patient with grade ≥3 elevation of increased amylase and lipase, which may be related to underlying gallstones). The rate of all grade and grade ≥3 rash observed was 24% and 0%, respectively, and the rate of all grade diarrhea and grade ≥3 observed was 22% and 0% respectively. Other grade 3 toxicities observed included increase alanine transaminase (0.8%), increased aspartate transaminase (0.8%), neutropenia (1.7%) and QT prolongation (1.7%). The ORR observed in patients with a T790M mutation (n = 48) was 29.2% and in patients without a T790M (n = 34) was 11.8%.

Adjuvant EGFR tyrosine kinase inhibitors

Given the activity of EGFR tyrosine kinase inhibitors in patients with activating *EGFR* mutant NSCLC in the metastatic setting, there is significant interest in investigating their role in the adjuvant setting. A single arm phase II trial investigated adjuvant erlotinib 150 mg daily for 2 years in surgical resected stage IA-IIIA patients

with *EGFR* mutant NSCLC (n=100); the primary end-point was 2-year disease free survival of at least 86% [7]. With a median follow-up of 3.4 years, the 2-year disease free survival observed was 89%, and the median disease free survival had not been reached. When the disease free survival curve is observed, there is an increased rate of recurrence after the 2-year time point when the erlotinib was discontinued, and the median time to recurrence after stopping erlotinib was 8.5 months (range 0–47). When treatment administration is assessed, 69% of patients completed at least 22 months of erlotinib, and 40% of patients required one dose reduction. A phase III trial investigated adjuvant erlotinib compared to placebo in patients with stage IB or IIIA NSCLC with EGFR protein expression by immunohistochemistry, or EGFR overexpression by fluorescence *in situ* hybridization (FISH) [8]. The primary end-point was disease-free survival, and secondary end-points were overall survival in the intent-to-treat subset, and disease-free survival and overall survival in the *EGFR* mutant subset using a hierarchical testing procedure. Patients assigned to erlotinib compared to placebo experienced a similar disease free survival (hazard ratio [HR] of 0.90; 95% CI, 0.741 to 1.104; $P = 0.3235$) and overall survival (HR of 1.13; 95% CI, 0.881 to 1.448; $P = 0.3350$). Patients received a median of 11.9 months of erlotinib (range 0.03 to 24.0). In the *EGFR* mutant NSCLC subset (n = 161), patients assigned to the erlotinib compared to placebo experienced a longer disease-free survival (HR of 0.61; 95% CI, 0.384 to 0.981, P=0.0391) but, due to the hierarchical testing procedure and the fact that the primary end-point was not met, this result is not considered statistically significant. Patients assigned to erlotinib compared to placebo experienced a similar overall survival (HR of 1.09; 95% CI, 0.545 to 2.161; $P = 0.8153$).

The discussion and questions related to these two trials was quite animated at the ASCO meeting, and the topics discussed were the optimal duration of therapy and dose of erlotinib, whether adjuvant erlotinib was delaying rather than preventing recurrence, and the potential use of erlotinib outside the context of the clinical trial. The National Cancer Institute (NCI) Adjuvant Lung Cancer Enrichment Marker identification and Sequencing Trial (ALCHEMIST) investigating adjuvant erlotinib in patients with *EGFR* mutant NSCLC with the primary end-point of overall survival will define the role of adjuvant erlotinib [9].

First-line therapy for EGFR mutant NSCLC

Two phase III trials compared afatinib to a platinum-doublet in patients with advanced *EGFR* mutant NSCLC, and a combined analysis for overall survival was presented at ASCO, as well as subset analyses based on *EGFR* mutation subtype (exon 19 deletion and exon 21 L858R point mutation) [10]. In the individual trials (LUX-Lung-3 and LUX-Lung-6), a significant improvement in overall survival for patients assigned to afatinib compared to chemotherapy was not observed, but an improvement in overall survival was observed for patients assigned to afatinib in the combined analysis (Table 1). In subgroup analysis based on *EGFR* mutation type the benefit appeared to be limited to patients with exon 19 mutations. When cross-over to EGFR tyrosine kinase inhibitor therapy was examined, 75% of patients who received cisplatin and pemetrexed received an EGFR tyrosine kinase inhibitor and 56% of patients who received cisplatin and gemcitabine received an EGFR tyrosine kinase inhibitor. The rate of second-line EGFR tyrosine kinase inhibitors in countries with insurance coverage was 91% and without insurance coverage was 52%.

The data suggest that first-line EGFR tyrosine kinase inhibitor therapy may provide an improved overall survival in patients with exon 19 mutations, and that patients with *EGFR* exon 19 mutations benefit more from EGFR tyrosine kinase inhibitor therapy than

Table 1. Overall survival of patients with common *EGFR* mutations (defined as exon 19 deletion and exon 21 L858R point mutation) in LUX-3, LUX-6, and combined cohorts [10]

Patient cohort	Afatinib (median OS)	Platinum-based chemotherapy (median OS)	Hazard ratio (95% confidence interval)
LUX-3 (n = 307)	31.6 months	28.2 months	0.78 (0.58-1.06) $P = 0.1090$
LUX-6 (n = 324)	23.6 months	23.5 months	0.83 (0.62-1.09) $P = 0.1756$
LUX-3 and LUX-6 (n = 631)	27.3 months	24.3 months	0.81 (0.66-0.99) $P = 0.0374$
LUX-3 and LUX-6 exon 19 (n = 355)	31.7 months	20.7 months	0.59 (0.45-0.77) $P = 0.0001$
LUX-3 and LUX-6 L858R (n = 276)	22.1 months	26.9 months	1.25 (0.92-1.71) $P = 0.1600$

EGFR, epidermal growth factor receptor; OS, overall survival.

patients with *EGFR* exon 21 mutations. Differences in outcomes between exon 19 and 21 mutations had been observed previously, and many trials stratify patients based on type of exon mutation [11,12]. The availability of second-line EGFR tyrosine kinase inhibitors appears to be associated with insurance policies, and trial designs that account for variable access to effective second-line therapies are required. The overall survival difference observed is most likely related to the larger size of this analysis compared to previous trials of EGFR tyrosine kinase inhibitors *vs*. platinum-based chemotherapy, rather than the specific activity of afatinib.

A randomized phase II trial compared erlotinib to erlotinib plus bevacizumab in patients with activating *EGFR* mutations (defined as exon 19 deletion and exon 21 L858R point mutations) and advanced stage NSCLC (n = 152) [13]. The primary end-point was progression-free survival by independent radiological review. Patients assigned to erlotinib with bevacizumab compared to erlotinib alone experienced a statistically significant improvement in progression-free survival (Table 2). The grade ≥3 adverse events observed at a higher rate in the erlotinib plus bevacizumab arm were hypertension (60% *vs*. 10%) and proteinuria (8% *vs*. 0%). When a subset analysis was performed, patients with exon 19 mutations (n = 80) assigned to the erlotinib plus bevacizumab arm, compared to the erlotinib alone arm, experienced a statistically significant improvement in progression-free survival, while patients with exon 21 mutations (n = 72) did not (Table 2). While the phase II results are promising, the combination of erlotinib and bevacizumab should be considered investigational and a confirmatory trial is ongoing.

ALK rearranged NSCLC

Currently crizotinib is approved by the United States Food and Drug Administration for patients whose tumors demonstrated an *ALK* rearrangement by FISH. Many clinicians currently use crizotinib as first-line therapy based on the numerically higher ORR and longer progression-free survival compared to historical data with platinum-based doublets. A phase III trial compared crizotinib to cisplatin or carboplatin and pemetrexed in patients with locally advanced or metastatic NSCLC with evidence of ALK rearrangement by central testing (n = 343) [14]. The primary end-point was progression-free survival by independent radiological review, and patients assigned to the chemotherapy arm were allowed to cross-over to crizotinib at the time of disease progression. Patients assigned to crizotinib compared to platinum-pemetrexed experienced a statistically significant improvement in progression-free survival (HR of 0.45, 95% CI, 0.35 to 0.60; $P<0.0001$; median 10.9 and 7.0 months, respectively) and ORR (74% *vs*. 45%, $P<0.0001$). No unexpected adverse events were observed in either treatment arm. This trial provides validation for the first-line use of crizotinib, and demonstrates the activity of the platinum-pemetrexed in this patient population.

Ceritinib (LDK378) is a novel ALK tyrosine kinase inhibitor that is a potent and selective ALK inhibitor that has demonstrated activity in patients who have previously received crizotinib and patients who are crizotinib naïve in the phase I and dose expansion cohort trial [15]. The dose cohort of ceritinib at 750 mg daily included 163 patients with *ALK* rearranged NSCLC who had previously been treated with ALK tyrosine kinase inhibitors and 83 who were ALK tyrosine kinase inhibitor naïve. The presentation data provided additional efficacy, toxicity, and tolerability data [16]. The ORR in the ALK tyrosine kinase inhibitor groups previously treated and naïve was 54.6% (95% CI, 46.6 to 62.4%) and 66.3% (95% CI, 55.1 to 76.3%), respectively. The median progression-free survival in the ALK tyrosine kinase inhibitor naïve and previously treated groups was non-estimable (95% CI, 8.31 to non-estimable) and 6.90 months (95% CI, 5.39 to 8.41), respectively. A subset analysis was performed on the patients with brain metastases at baseline (n = 124): 98 patients had previously received ALK tyrosine kinase

Table 2. Efficacy results of randomized phase II trial of erlotinib alone or with bevacizumab in patients with *EGFR* mutant NSCLC [13]

Efficacy end-point	Erlotinib and bevacizumab (n = 75)	Erlotinib (n = 77)	Hazard ratio or *P*-value (95% confidence interval)
Progression-free survival (n = 152)	Median: 16.0 months	Median: 9.7 months	0.54 (0.36-0.79) $P = 0.0015$
Objective response rate	69%	64%	$P = 0.4951$
Disease control rate	99%	88%	$P = 0.0177$
Exon 19 subset (n = 80)	Median: 18.0 months	Median 10.3 months	0.41 (0.24-0.72)
Exon 21 subset (n = 72)	Median 13.9 months	Median 7.1 months	0.67 (0.38-1.18)

EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer.

inhibitors and 10 of these had measurable intracranial disease; 26 patients were ALK tyrosine kinase inhibitor naïve and 4 of these had measurable intracranial disease. The ORR for intracranial metastases in the ALK tyrosine kinase inhibitor previously treated and naïve groups was 40% (95% CI, 12.2 to 73.8%) and 75% (95% CI, 19.4 to 99.4%), respectively. The ORR should be interpreted cautiously given the small numbers, but the data demonstrate activity of ceritinib in brain metastases. The rate of non-laboratory grade ≥3 adverse events observed in 255 patients were diarrhea (6%), nausea (4%), vomiting (4%), abdominal pain (2%), fatigue (5%), decreased appetite (1%), and interstitial lung disease (3%). The grade ≥3 laboratory adverse events observed in the 255 patients were anemia (5%), increased alanine transaminase (27%), increased aspartate transaminase (13%), increased creatinine (2%), hyperglycemia (13%), hypophosphatemia (7%), and increased lipase (10%). At least one dose reduction was required in 59% of patients, and 9% of patients discontinued treatment due to adverse events.

Squamous histology and second-line NSCLC

Patients with advanced disease NSCLC with squamous histology and a good performance status receive a platinum-based doublet as standard therapy and, despite numerous trials, the standard of care has remained the same for several decades. Necitumumab is a human anti-EGFR monoclonal antibody, and a phase III trial compared cisplatin and gemcitabine with and without necitumumab (n = 1.093) [17]. The primary end-point was overall survival, and secondary end-points were ORR, progression-free survival, toxicity, and an exploratory analysis of the H-score based on EGFR expression. Patients assigned to the necitumumab arm, compared to the platinum-based therapy alone, experienced a statistically significant improvement in overall survival and progression-free survival, but similar ORR (Table 3). The H-score was not predictive of overall survival or progression-free survival benefit. The grade ≥3 adverse events observed at higher rate in the necitumumab arm, compared to chemotherapy alone arm, were hypomagnesaemia (9.3% *vs*. 1.1%), and skin rash (7.1% *vs*. 0.4%). The rate of grade ≥3 arterial thromboembolic events in the necitumumab arm and chemotherapy alone arm was 3.9% and 2.0%, respectively, and the rate of grade ≥3 venous thromboembolic events was 5.0% and 2.6%, respectively.

Ramucirumab is a monoclonal antibody against VEGFR-2, and a phase III trial compared docetaxel with ramucirumab or placebo in patients who had progressed after platinum-based therapy (n = 1.253) [18]. The primary end-point was overall survival, and secondary end-points were progression-free survival, ORR, and toxicity. Patients with all histologies were eligible, and approximately 25% of patients enrolled had squamous histology. Patients assigned to docetaxel and ramucirumab, compared to docetaxel and placebo, experienced a statistically significant improvement in overall survival, progression-free survival, and ORR (Table 4). Patients assigned to the ramucirumab and docetaxel arm, compared to the docetaxel and placebo arm, experienced a higher rate of grade 3 or 4 neutropenia (48.8% *vs*. 39.8%), and febrile neutropenia (15.9% *vs*. 10%). However, the rates of grade ≥3 gastrointestinal hemorrhage, hemoptysis, and pulmonary hemorrhage were similar in the two arms.

Extensive stage small cell lung cancer

A previous phase III trial of prophylactic cranial irradiation, compared to observation, in ES-SCLC revealed a statistically significant reduction in the rate of symptomatic brain metastases and an improvement in overall survival [19]. This trial did not require routine imaging of the brain after completion of chemotherapy, and did not have a specified schedule of repeat brain imaging after completion of prophylactic cranial irradiation. A second phase III trial compared prophylactic cranial irradiation to observation in patients who had completed 4-6 cycles of platinum-based therapy and who had no evidence of

Table 3. Phase III trial of cisplatin and gemcitabine with and without necitumumab in patients with stage IIIB or IV non-small cell lung cancer with squamous histology [17]

Efficacy end-point	Cisplatin, gemcitabine and necitumumab (n = 545)	Cisplatin and gemcitabine (n = 548)	Hazard ratio or *P*-value (95% confidence interval)
Overall survival	11.5 months	9.9 months	0.84 (0.74-0.96) *P* = 0.012
Progression-free survival	5.7 months	5.5 months	0.85 (0.74-0.98) *P* = 0.020
Objective response rate	31.2%	28.8%	0.400
Disease control rate	81.8	77.0	0.043

Table 4. Phase III trial of docetaxel with and without ramucirumab for second-line treatment of non-small cell lung cancer [18]

Efficacy end-point	Docetaxel and ramucirumab (n = 628)	Docetaxel and placebo (n = 625)	Hazard ratio or *P*-value (95% confidence interval)
Overall survival	10.5 months	9.1 months	0.857 (0.751-0.979) *P* = 0.0235
Progression-free survival	4.5 months	3.0 months	0.762 (0.677-0.859) *P* < 0.0001
Objective response rate	22.9%	13.6%	<0.001
Disease control rate 64%	64.0%	52.6%	<0.001

brain metastases on radiological imaging [20]. The primary end-point was overall survival, and secondary end-points included time to brain metastases (evaluated with radiological imaging every 3 months), and progression-free survival. After a planned interim analysis, the trial was stopped because of futility by the independent data monitoring committee when 160 patients had been enrolled. Patients assigned to the prophylactic cranial irradiation arm, compared to the observation arm, had a trend towards worse overall survival (HR of 1.38, 95% CI, 0.95-2.02; median overall survival of 10.1 and 15.1 months, respectively). Patients assigned to prophylactic cranial irradiation had a longer time to development of brain metastases (P<0.001), and the rate of brain metastases at 12 months in the prophylactic cranial irradiation and observation arm was 32.4% and 58.0%, respectively. Patients assigned to prophylactic cranial irradiation and observation experienced a similar progression-free survival (HR of 1.12, 95% CI, 0.82-1.54; median 2.2 and 2.4 months, respectively). These two contradictory studies raise questions about the benefit of prophylactic cranial irradiation, and whether prophylactic cranial irradiation should be considered the standard of care for ES-SCLC.

Many patients with ES-SCLC will experience intrathoracic disease progression, which many times necessitates the use of palliative thoracic radiation therapy. The Chest Radiotherapy Extensive Stage Trial (CREST) randomized patients to thoracic radiation therapy (30 Gy in 10 fractions) or observation after 4–6 cycles of platinum-based therapy; patients in both arms received prophylactic cranial irradiation (n = 498) [21]. The primary end-point was overall survival, and a secondary end-point was local control. Patients assigned to thoracic radiation therapy compared to observation experienced a similar overall survival (HR of 0.84, 95% CI, 0.69-1.10; P=0.066). In an analysis of interaction of clinical factors with treatment for overall survival, no interaction between patients with intrathoracic disease at time of randomization and treatment was observed (P=0.35). Patients assigned to thoracic radiation therapy compared to observation experienced a statistically significant improvement in progression-free survival (HR of 0.73, 95% CI, 0.61-0.87; P = 0.001) and a lower rate of intrathoracic progression (43.7% *vs*. 79.8%, P<0.001).

Conclusion

There are several promising agents for patients with activating *EGFR* mutations who experience disease progression of an EGFR tyrosine kinase inhibitor and have a T790M resistance mutation, and multiple clinical trials will be available. Trials investigating adjuvant erlotinib in *EGFR* mutant NSCLC and comparing erlotinib to erlotinib plus bevacizumab in metastatic *EGFR* mutant NSCLC are ongoing. Crizotinib, when compared to platinum-pemetrexed, results in a superior ORR and progression-free survival in patients with *ALK* rearranged NSCLC, and ceritinib is a second-line option for this patient population, but patients need to be monitored closely for adverse events and the need for dose reductions. Necitumumab and ramucirumab demonstrated an improvement in overall survival in patient populations with limited options. There will undoubtedly be controversy about the potential role of these agents since the overall survival benefit observed in the phase III trials was modest. The role of prophylactic cranial irradiation and thoracic radiation therapy, two commonly used practices, will most likely be questioned based on the results of the recent phase III trials.

Abbreviations

ALK, anaplastic lymphoma kinase; ASCO, American Society of Clinical Oncology; CI, confidence interval; DLT, dose-limiting toxicity; EGFR, epidermal growth factor receptor; ES-SCLC, extensive stage small cell lung cancer; FISH, fluorescence *in situ* hybridization; HR, hazard ratio; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; ORR, objective response rate; VEGFR-2, vascular endothelial growth factor receptor 2.

Disclosures

The author has participated in advisory boards for Celgene, Genentech and Lilly Oncology.

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