How specific molecular-targeted agents can make obsolete a 'one size fits all' approach in *EGFR*-mutated NSCLC treatment (Review)

CARMEN POPESCU[1], LAURA MAZILU[2], ANDRA-IULIA SUCEVEANU[3] and ALEXANDRU GRIGORESCU[4]

[1]Doctoral School, 'Carol Davila' University of Medicine and Pharmacy, 050474 Bucharest; Departments of [2]Oncology and [3]Gastroenterology, Clinical Emergency Hospital, 'Ovidius' University, 900527 Constanţa; [4]Department of Oncology, 'Carol Davila' Clinical Nephrology Hospital, 'Carol Davila' University of Medicine and Pharmacy, 050474 Bucharest, Romania

Received June 9, 2021; Accepted July 9, 2021

DOI: 10.3892/etm.2021.10584

Abstract. Despite many advances in the latest period, lung cancer remains the cancer with the highest mortality. The latest developments concerning lung cancer treatment have changed the clinical practice by prolonging patient survival; however, unfortunately, there remains a high mortality rate firstly due to disease aggressivity and secondly through lack of early diagnosis and screening programs. Currently, researchers and clinicians are talking about personalized cancer treatment, and a complete diagnostic evaluation should consider, in addition to staging and histology, molecular aberrations, and genetics of the tumor tissue. The development of tyrosine kinase inhibitors (TKIs) has led to an improvement in survival for patients with EGFR mutations, this being the most studied driver mutation in adenocarcinoma; and at the same time an important predictive factor for patient outcome following the treatment with TKIs. Reseach must investigate the different TKI combination strategies in order to overcome resistance and to increase patient survival. Currently, there are ongoing clinical trials that will probably change the therapeutic approach for *EGFR*-mutated advanced or metastatic NSCLC patients.

Contents

1. Introduction

Despite many advances in the latest decade, lung cancer remains the cancer with the highest mortality, estimated at 1.8 million deaths annually, worldwide (1). The latest developments concerning lung cancer treatment have changed the clinical practice by bringing important advantages to patient survival; yet, unfortunately there remains a high mortality rate, firstly due to disease aggressivity and secondly through lack of early diagnosis and screening programs. There has been a global effort to reduce the incidence of lung cancer especially through tobacco control policies but despite all of these efforts, the worldwide incidence is increasing each year; in 2018 an estimated 2 million new cases of lung cancer worldwide were reported. Tabacco smoking remains the main cause of lung cancer but there is an increased incidence also in never smokers, this being considered a distinct entity with different molecular and genetic characteristics (1,2).

Latest therapeutic developments in lung cancer treatment include targeted agents and immunotherapy, as well as different combinations with complementary mechanisms of action.

Currently, there is discussion regarding personalized cancer treatment and there is no doubt that all diagnosed patients should have a specific diagnosis which will guide the tailored therapy

Correspondence to: Professor Laura Mazilu, Department of Oncology, Clinical Emergency Hospital, 'Ovidius' University, 124 Mamaia Boulevard, 900527 Constanţa, Romania
E-mail: lauragrigorov@gmail.com

Professor Andra-Iulia Suceveanu, Department of Gastroenterology, Clinical Emergency Hospital, 'Ovidius' University, 124 Mamaia Boulevard, 900527 Constanţa, Romania
E-mail: andrasuceveanu@yahoo.com

Abbreviations: BSC, best supportive care; CI, confidence interval; DCR, disease control rate; DOR, duration of response; EGFR, epidermal growth factor receptor; ESMO, European Society for Medical Oncology; HR, hazard ratio; ITT, intent-to-treat; NOS, not otherwise specified; NSCLC, non-small cell lung cancer; OS, overall survival; ORR, objective response rate; PFS, progression-free survival; TKIs, tyrosine kinase inhibitors

Key words: non-small cell lung cancer, tyrosine kinase inhibitors, EGFR mutations, target therapies, progression-free survival

in the lung cancer sequential treatment. A complete diagnostic evaluation should consider, in addition to staging and histology, the molecular aberrations and genetics of the tumor tissue.

In 2006, the treatment options for advanced non-small cell lung cancer (NSCLC) included platinum combination with gemcitabine, vinorelbine or taxanes, with an overall survival (OS) of 8 to 11 months (3). Later, histology driven pemetrexed for second line and targeted agent erlotinib in the front line were included in the European Society for Medical Oncology (ESMO) Treatment Guideline recommendations (4).

The development of tyrosine kinase inhibitors (TKIs) have led to an improvement in survival for patients with *EGFR* mutation, this being the most studied driver mutation in adenocarcinoma and at the same time an important predictive factor for patient outcome following the treatment with TKIs. The intracellular tyrosine kinase domain of *EGFR* is important in the transduction of the signal inside the cell and when a mutation or alteration occurs this leads to transformation in cell growth and development. Firstly, the tumors are classified according to their response to EGFR TKIs as sensitive, less sensitive, and resistant. The development of the TKI drug class has established a diversity of tumor genotypes and the multilateralism in the tumor response and evolution to TKI treatment (5,6).

In this work, an overview is presented of the class evolution of *EGFR* TKIs starting with 2006, and the main studies of EGFR TKIs in lung cancer are discussed.

2. First-generation TKIs

Gefitinib was first studied in phase III clinical trials on Asian patients whereas the genetic alteration on *EGFR* is more frequent in this population. IPASS trial enrolled 1,217 adenocarcinoma patients not previously treated for advanced or metastatic disease, who never smoked or had been light smokers, randomized in two open-label arms to receive either gefitinib or paclitaxel-carboplatin. Patients in the chemotherapy arm received 6 cycles while the other arm received gefitinib until disease progression. The primary endpoint was progression-free survival (PFS). The enrollment began in March 2006 and the cut-off date was April 2008, meeting the non-inferiority objective of PFS. Then the biomarker analysis was performed, and 59.7% of the samples were positive for a mutation at different exon levels (53.6% exon 19 deletions, 42.5% exon 21 mutation, 4.2% exon 20, 3.8% other, with patients presenting also multiple mutations). The final subgroup analyses showed a benefit in PFS (HR, 0.48; 95% CI, 0.36-0.64; P<0.001), with an objective response rate (ORR) of 71.2% for gefitinib compared with 47.3% for paclitaxel-carboplatin (P=0.001) (7). Later, in 2011 the final overall survival data was published together with biomarker analyses showing no difference in median OS between the two arms (18.8 vs. 17.4 months, HR, -0.90, P=0.109, 95% CI, 079-1.02) independent of the mutation status. The authors of the final analysis concluded that the *EGFR* mutation was a strong predictive biomarker for PFS and also for the response to treatment with gefitinib while not for OS; but also mentioning the high number of patients with cross-over to alternative TKI treatments in further lines (8).

In 2010, the WJTOG3405 clinical trial results were published. The study included 172 patients with *EGFR* mutation (involving exon 19 or 21) with NSCLC [97.1% adenocarcinoma, 1.16% adenosquamous and squamous carcinoma, 1.74%, not otherwise specified (NOS)] randomly assigned to receive either gefitinib or docetaxel plus cisplatin. The results showed a median PFS of 9.2 months in the gefitinib group, respectively 6.3 months in the comparison group (HR, 0.489; 95% CI, 0.336-0.710; P<0.0001) (9). Subsequently, in 2013, the results of phase IV clinical trial IFUM were communicated and published. This study included 106 patients with *EGFR* mutations from a total of 1,060 screened, all Caucasians, and 64.2% never-smokers. The study intended to demonstrate gefitinib efficacy in a non-Asian origin population. The ORR was 69.8%, the disease control rate (DCR) was 90.6%, the median PFS was 9.7 months, the median OS was 19.2 months, (95% CI, 17.0-not calculable, 27% maturity) (10).

Erlotinib was studied in several clinical trials in a front-line metastatic setting, firstly on an Asiatic population, the OPTIMAL study, then EURTAC including European patients. The OPTIMAL clinical trial compared erlotinib with gemcitabine plus cisplatin and included 165 NSCLC patients harboring *EGFR* mutations. Patients in the erlotinib arm were treated until progression, while in the other arm the therapy was continued up to 4 cycles. Median PFS was significantly longer in the erlotinib arm (13.1 vs. 4.6 months) in comparison to the doublet arm (HR, 0.16; 95% CI, 0.10-0.26; P<0.0001) (11).

EURTAC was the first clinical trial evaluating an *EGFR* TKI including exclusively European patients. The inclusion started in 2007 and finished in 2011 with enrollment of 174 patients with stage IIIB/IV NSCLC with *EGFR* mutatations, randomized 1:1 in two open-label arms. The study compared erlotinib with standard chemotherapy: cisplatin (or carboplatin) plus either docetaxel or gemcitabine. The results favored erlotinib with a difference in median PFS of 4.5 months (9.7 vs. 5.2 months) with an HR of 0.37, 95% CI, 0.25-0.54; P<0.0001 (12).

The above clinical trial results demonstrated higher efficacy of erlotinib and gefitinib in *EGFR*-mutated patients when compared with chemotherapy; yet, it should also be considered that the most frequent mutations were exon 19 and 21 mutations, and patients with brain metastasis were excluded. There was also a discussion regarding the past smokers' efficacy results. The EURTAC communicated HR for this subpopulation as 1.05. All the patients included in the above clinical trials in a front-line metastatic setting continued TKI treatment until disease progression, and this means that maintenance was also included.

Second-line studies involving first-generation TKIs consist of BR21 for erlotinib and phase III ISEL study including gefitinib. BR21 compared erlotinib in second-line metastatic NSCLC with a placebo. Erlotinib showed a significant difference in OS, the primary endpoint, of 6.7 vs. 4.7 months with a placebo (HR, 0.70; P<0.001) (13,14).

The ISEL study did not reach the primary endpoint, the OS in the overall population. It included 1,692 previously treated patients with NSCLC, randomized 2:1 to receive gefitinib or placebo plus best supportive care (BSC). There was no significant difference noted between the two arms concerning the median OS (5.6 vs. 5.1 months; HR, 0.89, 95% CI, 0.77-1.02; P=0.087) neither in the intent-to-treat (ITT) population nor in the adenocarcinoma subgroup (6.3 vs. 5.4 months; HR, 0.84; 95% CI, 0.68-1.03; P=0.089). Nevertheless, the preplanned analyses had positive results for never smokers (n=375; HR 0.67, P=0.012; median survival 8.9 vs. 6.1 months) and for the Asian population (n=342; HR, 0.66, P=0.01; median survival 9.5 vs. 5.5 months) (14).

3. Second-generation TKIs

The most common (90%) of the *EGFR* mutations include a deletion within exon 19 and Leu858Arg mutation in exon 21. Uncommon mutations include the substitution of G719X in exon 18, L861Q in exon 21, S768I in exon 20, and insertions in exon 20 (14). First-generation TKIs have demonstrated activity on the level of exons 19 and 21, but not on the other uncommon alterations.

ErbB family irreversible inhibitors, afatinib and dacomitinib, represent second-generation TKIs. Clinical activity of afatinib was assessed in Lux-Lung clinical trials, demonstrating activity in some uncommon mutations but in the meantime showing less benefit on others, such as *de novo* T790Met or the exon 20 insertion mutation (15). Lux Lung was an extensive clinical trial program including patients from the first-line to further lines of treatment, comparing afatinib with standard chemotherapy combination or first-generation TKI. The main efficacy results of the afatinib phase III clinical studies are summarized in Table I (16-21).

It is to be mentioned that all the above afatinib clinical trials included patients with asymptomatic brain metastasis. In Lux-Lung 3 and Lux-Lung 6, PFS was assessed for this populational subgroup with a value superiority but without statistical significance (11.1 vs. 5.4 months; HR, 0.54; P=0.1378, respectively, 8.2 vs. 4.7 months; HR, 0.47; P=0.106). Nevertheless, a meta-analysis of the two clinical trials showed a statistical difference in PFS of 2.8 months (8.2 vs. 5.4 months) with an HR of 0.5 and P=0.0297 for brain metastasis patients (17-19,22).

Dacomitinib also a second-generation *EGFR* TKI showed superiority compared with gefitinib in the phase III ARCHER 1050 trial which included 452 treatment naive patients, for advanced or metastatic disease with *EGFR* exon 19 deletions (59%) or exon 21 L858R mutation (41%). The majority of patients were never smokers (64.8%) and 74.9% had Asian ethnicity. Patients with brain metastasis were excluded. The PFS was 14.7 vs. 9.2 months for dacomitinib, respectively, gefitinib, with an HR of 0.59 (95% CI, 0.47-0.74; P<0.001). The ORR was similar between arms and the median OS was 34.1 months in the dacomitinib and 26.8 months in the gefitinib arm, with statistical significance (P=0.0438; HR, 0.76; 95% CI, 0.582-0.993) (23).

Patients receiving previously one or two lines of chemotherapy with advanced NSCLC presenting exon 19 or 21 activating mutations, were included in the ARCHER 1028 and ARCHER 1009 studies, randomized to receive either dacomitinib or erlotinib. The pooled analysis from both clinical trials showed a median PFS of 14.6 months for the investigational arm vs. 9.6 months in the erlotinib arm (HR, 0.71; two-sided log-rank, P=0.146). The median OS was 26.6 vs. 23.2 months (unstratified HR, 0.737; 95% CI, 0.431-1.259; two-sided log-rank, P=0.265) (24).

Dacomitinib showed superiority to gefitinib in survival and similar efficacy to erlotinib in patients harboring *EGFR* mutation with advanced/metastatic NSCLC, whereas afatinib failed to show any benefit in OS compared to first-generation TKI.

4. Third generation TKIs

Many patients acquire resistance during treatment with first- or second-generation of TKIs and 60% of patients develop a new mutation T790M (25). This has led to the development of new agents to overcome secondary resistance.

Table I. Efficacy results of afatinib phase III clinical studies.

Clinical trial (refs.)	Mutational status	Therapy	Line of treatment	Results	Statistical significance
Lux-Lung 1 phase IIB/III, 697 patients (16)	NA	Afatinib (50 mg/day) vs. placebo (2:1)	Further lines after erlotinib or gefitinib failure	mOS 10.8 vs. 12 months mPFS 3.3 vs. 1.1 months	P=0.74, HR 1.08, 95% CI, 0.86-1.35 P<0.0001, HR 0.38, 95% CI, 0.31-0.48
Lux-Lung 3 phase III, open-label 345 patients (17,18)	EGFR mutation	Afatinib (40 mg/day) vs. pemetrexed + cisplatin	First line	mPFS 11.1 vs. 6.9 months mOS 28.2 vs. 28.2 months	P=0.001, HR 0.58, 95% CI, 0.43-0.78 P=0.39, HR 0.88, 95% CI, 0.66-1.17
Lux-Lung 6 phase III, open-label 364 Asian patients (18,19)	EGFR mutation	Afatinib (40 mg/day) vs. gemcitabine + cisplatin	First line	mPFS 11.0 vs. 5.6 months mOS 23.1 vs. 23.5 months	P<0.0001, HR 0.28, 95% CI, 0.20-0.39 P=0.61, HR 0.93, 95% CI, 0.72-1.22
Lux-Lung 7 phase IIb, open-label 319 patients (20,21)	EGFR mutation (Del19 or L858R)	Afatinib vs. gefitinib	First line	mPFS 11.0 vs. 10.9 months mOS 27.9 vs. 24.5 months	P=0.017, HR 0.73, 95% CI, 0.57-0.95 P=0.258, HR 0.83, 95% CI, 0.66-1.12

EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; mPFS, median progression-free survival; mOS, median overall survival; HR, hazard ratio; CI, confidence interval.

Osimertinib, a selective irreversible third-generation TKI, established its place on the treatment sequencing for advanced NSCLC after the positive results of the phase III clinical trials FLAURA and AURA 3 (26,27).

The AURA 3, phase III clinical trial assessed the efficacy and safety of osimertinib when compared with combination platinum-chemotherapy. It included 419 patients with locally advanced or metastatic NSCLC positive for *EGFR* T790M who received first-line treatment with an *EGFR* tyrosine kinase inhibitor, randomized 2:1. Patients in the investigational arm received 80 mg osimertinib daily and in the comparison arm, pemetrexed with cisplatin or carboplatin, on a 21-day cycle. Maintenance pemetrexed treatment was permitted and treatment beyond progression was also allowed upon the investigator's decision. In the pemetrexed group, 60% of the patients crossed over and received osimertinib (27).

The primary endpoint was PFS assessed by the investigator and the secondary ones: OS and safety data. Median PFS was 10.1 months in the osimertinib arm vs. 4.4 months in the chemotherapy arm (HR, 0.30; 95% CI, 0.23-0.41; P<0.001) (27). Osimertinib did not demonstrate a statistically significant benefit in OS, with the median OS being 26.8 with osimertinib vs. 22.5 in the chemotherapy group (HR, 0.87; 95% CI, 0.67-1.12; P=0.277). Adjusted OS for crossover in the platinum doublet arm was 15.9 months (28).

The phase 3 osimertinib registration trial FLAURA included metastatic NSCLC patients presenting an *EGFR* mutation on exon 19 or 21-L858R and compared osimertinib efficacy with standard *EGFR* TKI in the first-line metastatic setting. The study showed a significant longer PFS with osimertinib compared with erlotinib or gefitinib (18.9 vs 10.2 months; HR, 0.46; 95% CI, 0.37-0.57; P<0.001); the ORR was similar between the arms and duration of response (DOR) was 17.2 vs. 8.5 months (27). The reported OS was 38.6 months for osimertinib and 31.8 months for the other TKI arm (HR, 0.80; 95.05% CI, 0.64-1.00; P=0.046) (29).

5. TKIs: Differences in efficacy by specific mutation type (exon 19del or exon 21 L858R)

Exon 19 deletion and exon 21 single point Leu858Arg mutations are the most common mutations, accounting together for 84.6% of the total *EGFR* sensitizing mutations (29). These subtypes are distinct in the response to *EGFR* TKIs according to their specific sensitivity coming from different molecular structures. Mutation in exon 19 is an in-frame deletion of amino acids, while in exon 21 the main alteration is a single-nucleotide substitution, leucine with arginine (30). Exon 19 mutation is associated with a more favorable prognosis in terms of PFS than exon 21 L858R substitution (31-35).

A meta-analysis including 4,835 patients from 26 clinical trials in which TKIs were compared with chemotherapy regimens showed a higher risk reduction for progression in the exon 19 deletion patient subgroups compared with the exon 21 L858R mutation (HR, 0.69; 95% CI, 0.57-0.82; P<0.001) (36).

6. Conclusions

EGFR mutations are of a wide variation, the most common being the exon 19 deletion and exon 21 L858R, with a higher incidence in the Asian population than in Caucasians. First- and second-generation TKIs have demonstrated benefit in PFS but have failed to show improvement in OS. The third-generation, osimertinib, showed improved median PFS as well as median OS and became the standard of care for patients harboring an *EGFR* mutation in the metastatic setting.

The question to be answered refers to different TKI combination strategies to overcome resistance and furthermore to increase survival. Ongoing clinical trials may change the therapeutic approach for patients with advanced or metastatic NSCLC with *EGFR* mutation.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

CP and LM were responsible for collected and assessing the literature data and the original draft preparation. All authors including AIS and AG were responsible for the final review of the literature data and manuscript editing. All authors read and approved the final manuscript for publication.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Authors' information

Author CP is a PhD student at the Doctoral School, 'Carol Davila' University of Medicine and Pharmacy, 050474 Bucharest, Romania.

References

1. Globocan data. https://www.uicc.org/news/globocan-2020-new-global-cancer-data. Accessed February 11, 2021.
2. de Groot PM, Wu CC, Carter BW and Munden RF: The epidemiology of lung cancer. Transl Lung Cancer Res 7: 220-233, 2018.
3. Rinaldi M, Cauchi C and Gridelli C: First line chemotherapy in advanced or metastatic NSCLC. Ann Oncol 17 (Suppl 5): v64-v67, 2006.
4. D'Addario G and Felip E; ESMO Guidelines Working Group: Non-small-cell lung cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 19 (Suppl 2): ii39-ii40, 2008.

5. Blume-Jensen P and Hunter T: Oncogenic kinase signalling. Nature 411: 355-365, 2001.
6. Zhou S, Hu X, Wang Y, Li J, Zhou L, Hao X, Liu Y and Shi Y: Clinicopathologic characteristics and outcome of patients with different EGFR mutations. Asia Pac J Clin Oncol 15: 166-171, 2019.
7. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, Sunpaweravong P, Han B, Margono B, Ichinose Y, *et al*: Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 361: 947-957, 2009.
8. Fukuoka M, Wu YL, Thongprasert S, Sunpaweravong P, Leong SS, Sriuranpong V, Chao TY, Nakagawa K, Chu DT, Nagahiro S, *et al*: Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS). J Clin Oncol 29: 2866-2874, 2011.
9. Mitsudomi T, Morita S, Yatabe Y, Negoro S, Okamoto I, Tsurutani J, Seto T, Satouchi M, Tada H, Hirashima T, *et al*: Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): An open label, randomised phase 3 trial. Lancet Oncol 11: 121-128, 2010.
10. Douillard JY, Ostoros G, Cobo M, Ciuleanu T, McCormack R, Webster A and Milenkova T: First-line gefitinib in caucasian EGFR mutation-positive NSCLC patients: A phase-IV, open-label, single-arm study. Br J Cancer 110: 55-62, 2014.
11. Zhou C, Wu YL, Chen G, Feng J, Liu XQ, Wang C, Zhang S, Wang J, Zhou S, Ren S, *et al*: Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): A multicentre, open-label, randomised, phase 3 study. Lancet Oncol 12: 735-742, 2011.
12. Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, Palmero R, Garcia-Gomez R, Pallares C, Sanchez JM, *et al*: Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): A multicentre, open-label, randomised phase 3 trial. Lancet Oncol 13: 239-246, 2012.
13. Shepherd FA, Pereira J, Ciuleanu TE, Tan EH, Hirsh V, Thongprasert S, Bezjak A, Tu D, Santabárbara P and Seymour L: A randomized placebo-controlled trial of erlotinib in patients with advanced non-small cell lung cancer (NSCLC) following failure of 1st line or 2nd line chemotherapy. A national cancer institute of Canada clinical trials group (NCIC CTG) trial. J Clin Oncol 22 (Suppl 14): S7022, 2004.
14. Thatcher N, Chang A, Parikh P, Rodrigues Pereira J, Ciuleanu T, von Pawel J, Thongprasert S, Tan EH, Pemberton K, Archer V and Carroll K: Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: Results from a randomised, placebo-controlled, multicentre study (iressa survival evaluation in lung cancer). Lancet 366: 1527-1537, 2005.
15. Zhang T, Wan B, Zhao Y, Li C, Liu H, Lv T, Zhan P and Song Y: Treatment of uncommon EGFR mutations in non-small cell lung cancer: New evidence and treatment. Transl Lung Cancer Res 8: 302-316, 2019.
16. Miller VA, Hirsh V, Cadranel J, Chen YM, Park K, Kim SW, Zhou C, Su WC, Wang M, Sun Y, *et al*: Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): A phase 2b/3 randomized trial. Lancet Oncol 13: 528-538, 2012.
17. Sequist LV, Yang JC, Yamamoto N, O'Byrne K, Hirsh V, Mok T, Geater SL, Orlov S, Tsai CM, Boyer M, *et al*: Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol 31: 3327-3334, 2013.
18. Yang JC, Wu YL, Schuler M, Sebastian M, Popat S, Yamamoto N, Zhou C, Hu CP, O'Byrne K, Feng J, *et al*: Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): Analysis of overall survival data from two randomised, phase 3 trials. Lancet Oncol 16: 141-151, 2015.
19. Wu YL, Zhou C, Hu CP, Feng J, Lu S, Huang Y, Li W, Hou M, Shi JH, Lee KY, *et al*: Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): An open-label, randomized phase 3 trial. Lancet Oncol 15: 213-222, 2014.
20. Park K, Tan EH, O'Byrne K, Zhang L, Boyer M, Mok T, Hirsh V, Yang JC, Lee KH, Lu S, *et al*: Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): A phase 2B, open-label, randomised controlled trial. Lancet Oncol 17: 577-589, 2016.
21. Paz-Ares L, Tan EH, O'Byrne K, Zhang L, Hirsh V, Boyer M, Yang JC, Mok T, Lee KH, Lu S, *et al*: Afatinib versus gefitinib in patients with EGFR mutation-positive advanced non-small-cell lung cancer: Overall survival data from the phase IIb LUX-Lung 7 trial. Ann Oncol 28: 270-277, 2017.
22. Schuler M, Wu YL, Hirsh V, O'Byrne K, Yamamoto N, Mok T, Popat S, Sequist LV, Massey D, Zazulina V and Yang JC: First-line afatinib versus chemotherapy in patients with non-small cell lung cancer and common epidermal growth factor receptor gene mutations and brain metastases. J Thorac Oncol 11: 380-390, 2016.
23. Mok TS, Cheng Y, Zhou X, Lee KH, Nakagawa K, Niho S, Lee M, Linke R, Rosell R, Corral J, *et al*: Improvement in overall survival in a randomized study that compared dacomitinib with geftinib in patients with advanced non-small cell lung cancer and EGFR-activating mutations. J Clin Oncol 36: 2244-2250, 2018.
24. Ramalingam S, O'Byrne K, Boyer M, Mok T, Jänne PA, Zhang H, Liang J, Taylor I, Sbar EI and Paz-Ares L: Dacomitinib versus erlotinib in patients with EGFR-mutated advanced nonsmall-cell lung cancer (NSCLC): Pooled subset analyses from two randomized trials. Ann Oncol 27: 423-429, 2016.
25. Westover D, Zugazagoitia J, Cho BC, Lovely CM and Paz-Ares L: Mechanisms of acquired resistance to first- and second-generation EGFR tyrosine kinase inhibitors. Ann Oncol 29 (Suppl 1): i10-i19, 2018.
26. Mok TS, Wu YL, Ahn MJ, Garassino MC, Kim HR, Ramalingam S, Shepherd FA, He Y, Akamatsu H, Theelen W, *et al*: Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. N Engl J Med 376: 629-640, 2017.
27. Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, Dechaphunkul A, Imamura F, Nogami N, Kurata T, *et al*: Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. N Engl J Med 378: 113-125, 2018.
28. Papadimitrakopoulou VA, Mok TS, Han JY, Ahn MJ, Delmonte A, Ramalingam SS, Kim SW, Shepherd FA, Laskin J, Hee Y, *et al*: Osimertinib versus platinum-pemetrexed for patients with EGFR T790M advanced NSCLC and progression on a prior EGFR-tyrosine kinase inhibitor: AURA3 overall survival analysis. Ann Oncol 31: 1536-1544, 2020.
29. Ramalingam SS, Vansteenkiste J, Planchard D, Cho BC, Gray JE, Ohe Y, Zhou C, Reungwetwattana T, Cheng Y, Chewaskulyong B, *et al*: Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC. N Engl J Med 382: 41-50, 2020.
30. Kobayashi Y and Mitsudomi T: Not all epidermal growth factor receptor mutations in lung cancer are created equal: Perspectives for individualized treatment strategy. Cancer Sci 107: 1179-1186, 2016.
31. Zhang Y, Sheng J, Kang S, Fang W, Yan Y, Hu Z, Hong S, Wu X, Qin T, Liang W and Zhang L: Patients with exon 19 deletion were associated with longer progression-free survival compared to those with L858R mutation after first-line EGFR-TKIs for advanced non-small cell lung cancer: A meta-analysis. PLoS One 9: e107161, 2014.
32. Lee CK, Wu YL, Ding PN, Lord SJ, Inoue A, Zhou C, Mitsudomi T, Rosell R, Pavlakis N, Links M, *et al*: Impact of specific epidermal growth factor receptor (EGFR) mutations and clinical characteristics on outcomes after treatment with EGFR tyrosine kinase inhibitors versus chemotherapy in EGFR-mutant lung cancer: A meta-analysis. J Clin Oncol 33: 1958-1965, 2015.
33. Sasaki H, Endo K, Takada M, Kawahara M, Kitahara N, Tanaka H, Okumura M, Matsumura A, Iuchi K, Kawaguchi T, *et al*: L858R EGFR mutation status correlated with clinico-pathological features of Japanese lung cancer. Lung Cancer 54: 103-108, 2006.
34. Jackman DM, Yeap BY, Sequist LV, Lindeman N, Holmes AJ, Joshi VA, Bell DW, Huberman MS, Halmos B, Rabin MS, *et al*: Exon 19 deletion mutations of epidermal growth factor receptor are associated with prolonged survival in non-small cell lung cancer patients treated with gefitinib or erlotinib. Clin Cancer Res 12: 3908-3914, 2006.
35. Hsu WH, Yang JCH, Mok TS and Loong HH: Overview of current systemic management of EGFR-mutant NSCLC. Ann Oncol 29 (Suppl 1): i3-i9, 2018.
36. Sheng M, Wang F, Zhao Y, Li S, Wang X, Shou T, Luo Y and Tang W: Comparison of clinical outcomes of patients with non-small-cell lung cancer harbouring epidermal growth factor receptor exon 19 or exon 21 mutations after tyrosine kinase inhibitors treatment: A meta-analysis. Eur J Clin Pharmacol 72: 1-11, 2016.