Overall survival in stage IV EGFR mutation-positive NSCLC: Comparing first-, second- and third-generation EGFR-TKIs (Review)

ASHOK K. VAID[1], ALOK GUPTA[2] and GAGANDEEP MOMI[3]

[1]Department of Medical Oncology, Medanta Cancer Institute, Gurugram, Haryana 122001;
[2]Department of Medical Oncology, Medanta Cancer Institute, Lucknow, Uttar Pradesh 226030;
[3]Department of Medical Affairs, Oncology, AstraZeneca Pharma India Ltd., Bangalore, Karnataka 560045, India

Received June 9, 2020; Accepted November 12, 2020

DOI: 10.3892/ijo.2021.5168

Abstract. A substantial (40-60%) proportion of patients with non-small cell lung carcinoma (NSCLC) have epidermal growth factor receptor (*EGFR*) mutations, a crucial therapeutic target in NSCLC. Treatment strategies for patients with advanced-stage NSCLC have markedly changed, from the empirical use of cytotoxic agents to targeted regimens. EGFR tyrosine kinase inhibitors (TKIs), the first-line therapy for advanced NSCLC, are reported to be the most effective. Although progression-free survival (PFS) and objective response rates have long been used as endpoints, meeting these endpoints may not necessarily coincide with an increase in overall survival (OS) among patients with advanced lung cancer. Recently, the FLAURA study with the third-generation, irreversible, oral EGFR-TKI, osimertinib, demonstrated an extended median OS by 6.8 months compared with standard EGFR-TKIs, with a 20% reduction in the risk of mortality [osimertinib, 38.6; EGFR-TKIs, 31.8; hazard ratio (HR), 0.80; 95% confidence interval (CI), 0.641-0.997; P=0.046]; this was in addition to meeting the primary endpoint of clinically and statistically significant PFS. Osimertinib was also shown to lead to a statistically significant reduction in the risk of central nervous system disease progression (HR, 0.48; 95% CI, 0.26-0.86; P=0.014). Notably, 28% of patients remained on osimertinib treatment for 3 years, considerably longer than those in the comparator group (9%). The duration of first subsequent treatment with osimertinib was 25.5 months compared with 13.7 months with standard EGFR-TKIs (HR, 0.478; 95% CI, 0.393-0.581; P<0.0001). Thus, the long-term OS benefit with first-line osimertinib highlights a promising option in the management of stage IV NSCLC. The present narrative review compares the OS benefit of first-, second- and third-generation EGFR-TKIs for patients with stage IV EGFR mutation-positive NSCLC and discusses their role in disease management.

Correspondence to: Dr Ashok K. Vaid, Department of Medical Oncology, Medanta Cancer Institute, CH Baktawar Singh Road, Sector 38, Gurugram, Haryana 122001, India
E-mail: ashok.vaid@medanta.org

Abbreviations: AEs, adverse events; ALK, anaplastic lymphoma kinase; CNS, central nervous system; *EGFR*, epidermal growth factor receptor; HR, hazard ratio; IPASS, Iressa Pan-Asia Study; TKI, tyrosine kinase inhibitors; ESMO, European Society for Medical Oncology; FDA, food and drug administration; NCCN, National Comprehensive Cancer Network; NSCLC, non-small cell lung carcinoma; OR, odds ratio; ORR, objective response rates; OS, overall survival; PFS, progression-free survival; SoC, standard of care

Key words: CNS efficacy, EGFR-TKI, non-small cell lung cancer, overall survival, osimertinib

Contents

Introduction

Recent progress in the molecular biology of non-small cell lung cancer (NSCLC) has led to the identification of diverse molecular mutations based on driver oncogenes, such as epidermal growth factor receptor (*EGFR*) and anaplastic lymphoma kinase (*ALK*) translocation. *EGFR* is one of the most common mutations, and a crucial therapeutic target in NSCLC. Sensitizing mutations in exon 21 (L858R exon 21-point mutation) and exon 19 (exon 19 deletions) activate the tyrosine kinase domain in *EGFR*, which promote the continuous uncontrolled cell growth, proliferation and

metastasis of tumor cells in NSCLC. The prevalence of EGFR mutation (EGFRm) is lower among Caucasian (15-18%) than among Asian (36-40%) and Indian (22-26%) populations (1-3).

EGFR-tyrosine kinase inhibitors (TKIs) demonstrate clinical responsiveness by potentially blocking the cell signaling pathways responsible for EGFR-mutated tumor cell growth (4). The first- and second-generation EGFR-TKIs have exhibited efficacy as first-line therapy for patients with NSCLC with EGFRm; however, the emergence of resistance in patients is inevitable (5,6). The T790M mutation in exon 20 of *EGFR* is the most common (50-70% of tumors) mechanism for secondary resistance to first-line EGFR-TKIs (7,8). In addition, human epidermal growth factor receptor (HER2) amplification and HER2 mutation have also been reported in a subset of EGFR-TKI-resistant lung tumors (9). Osimertinib is a third-generation, irreversible, oral EGFR-TKI that potently and selectively inhibits both EGFRm and EGFR T790M. It has demonstrated efficacy in NSCLC with central nervous system (CNS) metastases (10). Previous clinical trials on EGFR-TKIs have primarily focused on response rates and progression-free survival (PFS) as endpoints in NSCLC. Although, currently approved first-, second-, and third-generation EGFR-TKIs have demonstrated favorable response rates and PFS in NSCLC, the overall survival (OS) benefits have been marginal with most of the TKIs (11). OS, historically considered as the gold standard endpoint for establishing the efficacy in medical oncology due to its objectivity, reliability and precision, is defined as the time from randomization to mortality (12). An increase in PFS may not necessarily result in an increase in OS among patients with locally advanced or metastatic NSCLC. However, recent developments with the use of third-generation TKIs have provided promising results in terms of OS benefits in NSCLC. The present narrative review compares the OS benefits of first-, second- and third-generation EGFR-TKIs for patients with stage IV EGFRm NSCLC and discusses their role in disease management. Relevant publications in the English language that reported the clinical efficacy and safety of EGFR-TKIs were identified by searching the PubMed, Google Scholar and Embase databases. Articles on clinical trials and real-world evidence, along with publications from major oncology societies, such as European Society of Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN), were included in the present review.

Role of TKIs in the treatment of stage IV EGFR-mutated NSCLC. Treatment algorithms for NSCLC have markedly changed over the past few years with the introduction of targeted therapies. The current scenario of treatment for stage IV NSCLC will continue to evolve with emerging clinical and preclinical data explaining the mechanisms responsible for the observed clinical outcomes. The treatment algorithm for stage IV NSCLC with EGFR-activating mutation as recommended by the ESMO 2019 and NCCN 2020 guidelines is presented in Fig. 1 (13,14).

2. First- and second-generation EGFR-TKIs vs. chemotherapy

The first-generation TKIs, including gefitinib and erlotinib, interrupt *EGFR* signaling by blocking receptor tyrosine kinase activity by reversibly binding at or near the adenosine triphosphate binding site on the intracellular kinase domain. Second-generation TKIs, including afatinib and dacomitinib, are irreversible inhibitors, which bind covalently to the tyrosine kinase site. Several articles have elaborated the mechanisms of action and individual characteristics of EGFR-TKIs in detail (11,15,16). Gefitinib received an accelerated approval by the United States Food and Drug Administration (FDA) in 2003 as a monotherapy for NSCLC following the failure of both platinum-based and docetaxel chemotherapies based on the results from Iressa Pan-Asia Study (IPASS) and NEJ002 study (Table I) (17,18,22). Similarly, the EURTAC and ENSURE trials reported a better response rate and PFS with erlotinib compared with standard chemotherapy (Table I) (26,28). The LUX-Lung 3 and LUX-Lung 6 trials demonstrated a significantly longer PFS with afatinib compared with chemotherapy (Table I) (29,31). Table I shows the landmark trials and clearly demonstrates superior objective response rate (ORR), and PFS with EGFR-TKIs compared with former standard treatment of chemotherapy.

LUX lung 7, a global randomized trial, revealed the superiority of afatinib compared with gefitinib as the first-line treatment in terms of improved PFS and time to treatment failure. The ARCHER 1050 study reported a favorable PFS for dacomitinib compared with gefitinib. A higher magnitude of PFS benefit was observed with dacomitinib as demonstrated in the ARCHER 1050 study (Table II) (34,36).

Overall survival with first- and second-generation TKIs. Despite the PFS benefit, a greater number of clinical trials for first- and second-generation EGFR-TKIs have reported either a null or a marginal benefit for OS compared with chemotherapy. The NEJ002 trial reported a similar median OS for gefitinib and carboplatin-paclitaxel [27.7 months vs. 26.6 months; hazard ratio (HR), 0.887; P=0.483], whereas the EURTAC trial revealed a marginal (not statistically significant) OS benefit with erlotinib vs. chemotherapy [22.9 months vs. 19.6 months; HR, 0.92; 95% confidence interval (CI), 0.63-1.35; P=0.68] (Table I) (23,27). The LUX-Lung 3 (HR, 0.78; 95% CI, 0.58-1.06; P=0.11) and LUX-Lung 6 (HR, 0.83; 95% CI, 0.62-1.09; P=0.18) trials did not demonstrate an improved OS with afatinib compared with standard chemotherapy (Table I) (30). The LUX-Lung 7 study revealed that the median OS was numerically higher favoring afatinib (27.9 months), albeit not statistically significant when compared with gefitinib (25.0 months) (HR, 0.86; P=0.2580) (Table II) (35). The ARCHER 1050 study assessed dacomitinib compared with gefitinib in treatment-naïve patients and reported a median OS of 34.1 months with dacomitinib and 26.8 months with gefitinib, with an estimated HR of 0.760 (95% CI, 0.582-0.993; P=0.044) (Table II) (37). However, the endpoint of OS was third in hierarchy for statistical analysis following PFS and ORR. In addition, although the study demonstrated a significant PFS benefit compared with the control group, the ORR endpoint was not met. Hence, this OS benefit cannot be considered significant per the hierarchical approach of hypothesis testing. The United States FDA also reported that the findings of ARCHER 1050 were not consistent with an improvement in OS for dacomitinib (38). The improvement in OS may be the effect of subsequent therapy

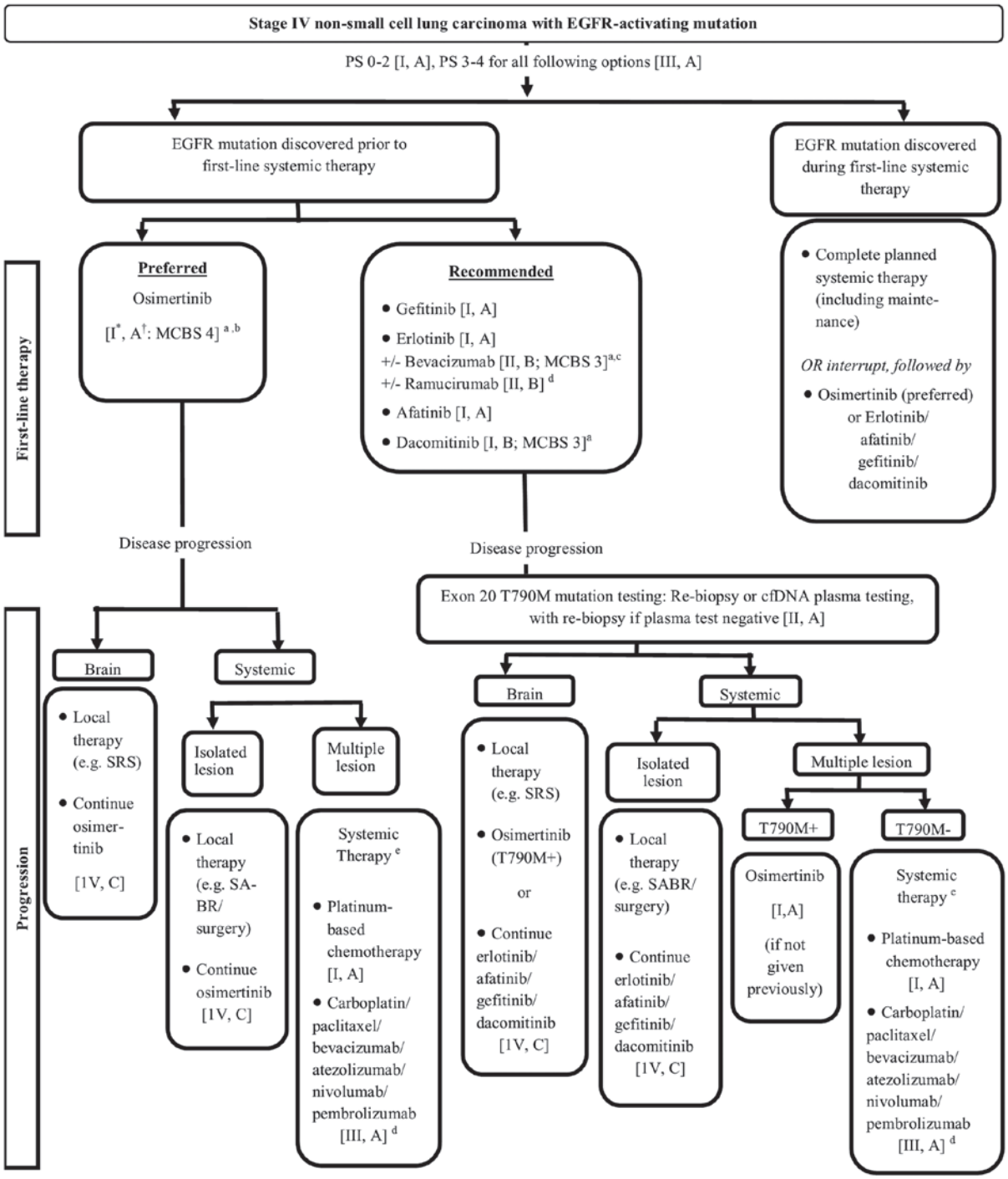

Figure 1. Treatment algorithm for stage IV NSCLC with EGFR-activating mutation. The figure has been recreated from the European Society for Medical Oncology (ESMO) 2019 and National Comprehensive Cancer Network (NCCN) 2020 guidelines (13,14). The asterisk symbol (*) indicates levels of evidence as follows: I, evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity; II, small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity; III, prospective cohort studies; IV, retrospective cohort studies or case-control studies; V, studies without a control group, case reports, or expert opinions. The '†' symbol indicates grades of recommendation as follows: A, strong evidence of efficacy with a substantial clinical benefit, strongly recommended; B, strong or moderate evidence of efficacy but with a limited clinical benefit, generally recommended; C, insufficient evidence of efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs), optional; D, moderate evidence against efficacy or for adverse outcome, generally not recommended; E, strong evidence against efficacy or for adverse outcome, never recommended. The lowercase letters indicate the following: a, ESMO-MCBS v1.1 score for new therapy/indication approved by the EMA since 1 January 2016; b, preferred option; c, MCBS score for the combination of bevacizumab with gefitinib or erlotinib; d, mot EMA-approved. PS, performance status; cfDNA, cell-free DNA; EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; MCBS, ESMO-Magnitude of Clinical Benefit Scale; SRS, Stereotactic radiosurgery; SABR; stereotactic ablative radiotherapy.

following the discontinuation of study drugs, approximately 50% of patients from the dacomitinib group and 62% from the gefitinib group received additional treatment, primarily chemotherapy, whereas few patients received third-generation

Table I. Efficacy of first- and second-generation EGFR TKIs in patients with EGFRm NSCLC.

Name of study	Study design	Intervention arms	ORR (%)	Median PFS (months)	Median OS (months)	(Refs.)
IPASS	Randomized, phase 3 trial, open-label, parallel-group	First-line gefitinib vs. carboplatin + paclitaxel	Gefitinib: 71.2%; carboplatin + paclitaxel: 47.3% (P<0.001)	Gefitinib: 9.5; carboplatin + paclitaxel: 6.3; HR, 0.48; 95% CI, 0.36-0.64; P<0.001	Gefitinib: 21.6; carboplatin + paclitaxel: 21.9; HR,1.00; 95% CI, 0.76-1.33; P=0.99	(18,19)
WJTOG 3405	Randomized, open-label	First-line gefitinib vs. cisplatin + docetaxel	Gefitinib: 62.1%; cisplatin + docetaxel: 32·2% (P<0.0001)	Gefitinib: 9.2; cisplatin + docetaxel: 6.3; HR, 0.49; 95% CI, 0.336-0.710; P<0.0001	Gefitinib: 34.9; cisplatin + docetaxel: 37.3; HR, 1.252; 95% CI, 0.883-1.775; P=0.20	(20,21)
NEJ002	Randomized, phase 3 trial	First-line gefitinib vs. carboplatin + paclitaxel	Gefitinib: 73.7%; carboplatin + paclitaxel: 30.7% (P<0.001)	Gefitinib: 10.8; carboplatin + paclitaxel: 5.4; HR, 0.30; 95% CI, 0.22-0.41; P<0.001	Gefitinib: 27.7; carboplatin + paclitaxel: 26.6; HR, 0.887; P=0.483	(22,23)
OPTIMAL	Phase 3, open-label, randomized study	First-line erlotinib vs. gemcitabine + carboplatin	Erlotinib: 83% Gemcitabine + carboplatin: 36% P<0.0001	Erlotinib 13.1; gemcitabine + carboplatin 4.6; HR, 0.16; 95% CI, 0.10-0.26; P<0.0001	Erlotinib: 22.8 gemcitabine + carboplatin: 27.2; HR, 1.19; 95% CI, 0.83-1.71; P=0.2663	(24,25)
EURTAC	Open-label, randomized phase 3 trial	Erlotinib vs. Cisplatin + docetaxel or gemcitabine	CR: erlotinib, 3%; PR: erlotinib, 61%; Chemotherapy, 18%; OR, 7.5; 95% CI, 3.6-15.6; P<0.0001	Erlotinib: 9.7; chemotherapy, 5.2; HR, 0.37; 95% CI, 0.25-0.54; P<0.0001	Erlotinib: 22.9; chemotherapy, 19.6; HR, 0.92; 95% CI, 0.63-1.35; P=0.68	(26,27)
ENSURE	Open-label, randomized, phase 3 study	Erlotinib vs. gemcitabine/cisplatin	Erlotinib, 62.7%; gemcitabine/cisplatin, 33.6%	Erlotinib, 11; gemcitabine/cisplatin, 5.5; HR, 0.34; 95% CI, 0.22-0.51; log-rank (P<0.0001)	Erlotinib, 26.3; gemcitabine/cisplatin, 25.5; HR, 0.91; 95% CI, 0.63-1.31; P=0.607	(28)
LUX-Lung 3	Open-label, randomized, phase 3 study	Afatinib vs. cisplatin + pemetrexed	Afatinib, 56%; cisplatin + pemetrexed, 23%; P=0.001	Afatinib, 11.1; cisplatin + pemetrexed, 6.9; HR, 0.58; 95% CI, 0.43-0.78; P=0.001	Afatinib, 31.6; cisplatin + pemetrexed, 28.2; HR, 0.78; 95% CI, 0.58-1.06; P=0.11	(29,30)
LUX-Lung 6	Open-label, randomized phase 3 trial	Afatinib vs. cisplatin + gemcitabine	Afatinib, 66.9%; cisplatin + gemcitabine, 23.0%; OR, 7.28; 95% CI, 4.36-12.18; P<0.0001	Afatinib, 11.0; cisplatin + gemcitabine; 5.6; HR, 0.28; 95% CI, 0.20-0.39; P<0.0001	Afatinib, 23.6; cisplatin + gemcitabine, 23.5; HR, 0.83, 95% CI, 0.62-1.09; P=0.18	(30,31)

Table I. Continued.

Name of study	Study design	Intervention arms	ORR (%)	Median PFS (months)	Median OS (months)	(Refs.)
AURA3	Randomized, open-label, phase 3 trial	Second-line osimertinib vs. platinum + pemetrexed after first-line EGFR-TKI therapy	Osimertinib, 71%; platinum + pemetrexed, 31% OR, 5.39, 95% CI, 3.47 to 8.48, P<0.001	Osimertinib, 10.1; platinum + pemetrexed, 4.4; HR, 0.30; 95% CI, 0.23-0.41; P<0.001; median PFS CNS metastases: Osimertinib, 8.5; platinum + pemetrexed, 4.2; HR, 0.32; 95% CI, 0.21-0.49	Osimertinib, 26.8; platinum + pemetrexed, 22.5; HR, 0.87, 95% CI, 0.67-1.12; P= 0.277	(32,33)

CI, confidence interval; CNS, central nervous system; CR, complete response; EGFR TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; HR, hazard ratio; NA, not available; NSCLC, non-small cell lung cancer; OR, odds ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response.

EGFR-TKIs as subsequent therapy (osimertinib, olmutinib, rociletinib, avitinib and unspecified EGFR-TKIs). The patients receiving subsequent third-generation EGFR-TKIs appeared to survive longer than patients who received chemotherapy.

Challenges with first- and second-generation TKIs. Resistance, brain metastasis and adverse events (AEs). Despite the initial benefit, in at least half of patients treated with first- and second-generation EGFR-TKIs, disease ultimately progresses (after a median of 10-14 months) due to acquired resistance, primarily in patients with the T790M mutation encoded by exon 20 of EGFR (Tables I and II) (20,22,29,31,34,37). The T790M mutation occurs in approximately 50-70% of tumors with acquired resistance to EGFR-TKIs (7,8,39-43). Other biological resistance mechanisms include MET amplification, EGFR amplification, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) amplification, HER2 amplification and histological transformation to small cell lung cancer (44). Alongside the challenge of resistance, a significant proportion of patients with EGFRm NSCLC (25%) exhibit brain metastases at diagnosis, which further escalates during the course of disease (45), leading to poor survival with significant impairments in the quality of life (46,47). An insufficient crossing of EGFR-TKIs to sanctuary sites in CNS is a crucial deficiency resulting in disease progression in CNS with first- and second-generation EGFR-TKIs. In patients carrying CNS metastases, both first- and second-generation EGFR-TKIs exhibit limited efficacy due to the inadequate ability to penetrate the blood-brain barrier, leading to low concentrations in the cerebrospinal fluid and the relapse of CNS metastases (48-51). Unfavorable toxicity profile with AEs, including but not limited to, fatigue, rash, stomatitis, diarrhea and elevated levels of alanine aminotransferase, is yet another challenge associated with first- and second-generation TKIs and may warrant dose reduction or drug discontinuation (11). The higher toxicity to first- and second-generation EGFR-TKIs is attributed to their higher affinity for the wild-type EGFR. A comparative overview of the AEs for different EGFR-TKIs has been provided in the studies by Doval *et al* (52), and Shah and Shah (53).

3. Third-generation EGFR-TKIs

The limitations associated with first- and second-generation EGFR-TKIs have paved the way for the development of third-generation EGFR-TKIs, including osimertinib. The third-generation agents are pyrimidine-based compounds designed to target *EGFR* activating the T790M mutation in a selective and irreversible manner, facilitating improved potency, better safety and superior penetration into sanctuary sites in CNS compared with earlier-generation EGFR-TKIs (54). These TKIs exhibit better tolerance and a lower epithelial toxicity due to poor wild-type *EGFR* activity compared with earlier-generation EGFR-TKIs (55,56). Osimertinib inhibits *EGFR* carrying T790M, del19 and L858R mutations, with least activity against the wild-type *EGFR*. Evidence from pre-clinical studies has also demonstrated the antitumor efficacy of osimertinib against multiple HER2 aberrations in lung cancer, either as a single agent or in combination with the BET inhibitor JQ1 (57).

Table II. Head-to-head comparison of first- and second-generation EGFR TKIs in patients with EGFR mutation-positive NSCLC.

Name of study	Study design	Intervention arms	ORR (%)	PFS (months)	Median OS	(Refs.)
LUX-Lung 7	Open-label, randomized controlled phase 2B	First-line afatinib vs. gefitinib	Afatinib, 70%; gefitinib, 56%; OR, 1.87; 95% CI, 1.18-2.99; P=0.00830	Afatinib, 11.0; gefitinib, 10.9; HR, 0.73; 95% CI, 0.57-0.95; P=0.017	Afatinib, 27.9; gefitinib, 24.5; HR, 0.86; 95% CI, 0.66-1.12; P=0.2580 (NS)[a]	(34,35)
ARCHER 1050	Randomized, open-label, phase 3	First-line dacomitinib vs. gefitinib	Dacomitinib, 74.9%; gefitinib, 71.6%	Dacomitinib, 14.7; gefitinib, 9.2; HR, 0.59; 95% CI, 0.47-0.74; P<0.001	Dacomitinib, 34.1; gefitinib, 26.8; HR, 0.760; 95% CI, 0.582-0.993; P=0.044 (NS)[a]	(36,37)
FLAURA	Double-blind phase 3	First-line osimertinib vs. gefitinib or erlotinib	Osimertinib, 80%; gefitinib, 76%; OR, 1.27; 95% CI, 0.85-1.90; P=0.24	Osimertinib, 18.9; gefitinib, 10.2; HR, 0.46; 95% CI, 0.37-0.57; P<0.001	Osimertinib, 38.6; gefitinib, 31.8; HR, 0.799 (0.641, 0.997); P=0.0462 (S)[b]	(64,71)

[a]Endpoint of OS was third in hierarchy for statistical analysis following PFS and ORR, although that study demonstrated a significant PFS gain than control group, the ORR endpoint was not met. Hence, this OS benefit cannot be considered significant per the hierarchical approach of hypothesis testing. CI, confidence interval; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; HR, hazard ratio; OS, overall survival; OR, odds ratio; ORR, objective response rate; PFS, progression-free survival; NS, not significant; [b]S, significant.

Initially, osimertinib received accelerated approval by the FDA (2015) for T790M mutation-positive NSCLC following resistance to first-line EGFR-TKI therapy based on promising evidence from the AURA1 and AURA2 studies (58-61). The AURA3 study demonstrated the superior efficacy and safety of osimertinib compared with pemetrexed plus carboplatin or cisplatin following progression with first-line EGFR-TKIs. The median PFS was significantly longer with osimertinib than with chemotherapy (10.1 vs. 4.4 months; HR, 0.30; P<0.001) (Table I) (32). Based on these results, osimertinib received regular approval from the FDA (2017) for disease progression on or after EGFR-TKI therapy (62). Furthermore, the AURA3 study also revealed a longer time to deterioration of key symptoms and a higher improvement in the global health status or quality of life of patients treated with osimertinib than with chemotherapy (63). In line with the AURA studies, the FLAURA study revealed a higher PFS with osimertinib compared with standard of care (SoC) (18.9 months vs. 10.2 months; HR, 0.46; P<0.001), maintained consistently across all subgroups (including race and different mutation types) (Table II) (64). This led to its approval as the first-line treatment for metastatic NSCLC with *EGFR* exon 19 deletions or exon 21 L858R mutations (65). Consistent with the overall FLAURA results, a subset of the Asian population demonstrated clinically meaningful efficacy outcomes and a better safety profile for osimertinib compared with the SoC EGFR-TKI group (higher median PFS, 16.5 months vs. 11.0 months; HR, 0.54; P<0.0001), higher ORR (80 vs. 75%) and fewer AEs of grade 3 or higher (40 vs. 48%) (66). The OS data for osimertinib were immature when it received approval from the FDA; however, the OS was continuously monitored. The two endpoints of OS and CNS PFS were tested after the primary PFS analysis in a hierarchical procedure at the time of PFS analysis.

4. Overall survival with osimertinib

Currently, robust data demonstrating the benefits of OS with EGFR-TKIs are limited. Recent accelerated drug approvals have been primarily based on ORRs and PFS. Although PFS is considered as the designated surrogate endpoint for OS, its validity has been questioned due to the high risk of bias, particularly when the magnitude of the PFS benefit is minimal (67,68). OS is precise and easily measurable and provides an unambiguous yardstick to evaluate efficacy. Furthermore, OS is a reliable endpoint with a standardized definition and no risk of bias, and it does not require any validated instrument or frequent radiological assessment (69). Hence, continued OS monitoring is crucial to demonstrate direct clinical benefit of any drug. International bodies, such as the American Society of Clinical Oncology, have highlighted the need for clinically meaningful outcomes, including OS, quality of life and the AE profile in order to ensure accurate treatment effects (70). Mature data from the FLAURA study revealed a statistically significant and clinically meaningful improvement in OS with osimertinib (71). This is the first time an EGFR-TKI has translated PFS to a significant OS benefit. The median OS in the osimertinib group was extended by 6.8 months, representing a 20% reduction in the risk of mortality

(osimertinib, 38.6; 95% CI, 34.5-41.8 vs. standard EGFR-TKIs 31.8; 95% CI, 26.6-36.0; HR for mortality, 0.80; 95% CI, 0.64-1.00; P=0.046) (71). The OS results for osimertinib and comparator EGFR-TKIs at months 12, 24 and 36 were as follows: Month 12, 89 vs. 83%; month 24, 74 vs. 59%; and month 36, 54 vs. 44%. In addition, there was an improvement in OS with osimertinib across the key patient subgroups. However, the benefit varied in different subgroups, and the largest numerical between-group differences were observed between Asian and non-Asian patients (71) (Table III). Recent evidence from the AURA3 study reported no statistically significant benefit in the OS of patients with advanced NSCLC with the T790M mutation for osimertinib vs. pemetrexed plus carboplatin or cisplatin (median OS, 26.8 vs. 22.5 months; HR, 0.87; 95% CI, 0.67-1.12; P=0.277), possibly reflecting the high crossover rate (73%) of patients from platinum-pemetrexed to osimertinib (Table I) (33). The analysis after crossover adjustment revealed an HR of 0.54 (95% CI, 0.18-1.6). However, the time to first subsequent therapy or mortality revealed a clinically meaningful advantage towards osimertinib (HR, 0.21; 95% CI, 0.16-0.28; P<0.001) (33).

Table III. Hazard ratios for overall survival among subgroups in the FLAURA study.

Subgroup	Hazard ratio (95% CI)
Sex	
Male	0.79 (0.55-1.14)
Female	0.79 (0.60-1.04)
Age	
<65 years	0.72 (0.54-0.97)
≥65 years	0.87 (0.63-1.22)
Race	
Asian	1.00 (0.75-1.32)
Non-Asian	0.54 (0.38-0.77)
CNS metastases at trial entry	
Yes	0.83 (0.53-1.30)
No	0.79 (0.61-1.01)
WHO performance status	
0	0.93 (0.63-1.37)
1	0.70 (0.54-0.91)
EGFR mutation at randomization	
Exon 19 deletion	0.68 (0.51-0.90)
L858R	1.00 (0.71-1.40)

A hazard ratio of <1.00 indicates a lower risk of death with osimertinib than with the comparator EGFR-TKI. CI, confidence interval; CNS, central nervous system; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor. The table was reproduced from the data of a previous study (39).

5. CNS efficacy of osimertinib in patients with advanced NSCLC

Previous studies, such as the LUX-Lung 3 and 6 studies have primarily assessed systemic PFS in patients with NSCLC carrying the EGFRm with CNS metastasis. Osimertinib is the first EGFR-TKI to be evaluated for both systemic and intracranial PFS in patients with CNS metastasis. The AURA3 study demonstrated a longer PFS (8.5 vs. 4.2 months), a better CNS response rate (70 vs. 31%) and a longer duration of response (8.9 vs. 5.7 months) with osimertinib compared to chemotherapy in patients with CNS metastases (72). Similarly, the FLAURA study revealed a longer CNS PFS (irrespective of T790M) with osimertinib than with standard EGFR-TKIs (gefitinib or erlotinib), which increased the time patients with CNS metastases lived without CNS disease progression or time to mortality (median CNS PFS was not reached with osimertinib and was 13.9 months with standard EGFR-TKI therapy), alongside a reduced risk of CNS progression by 52%; (HR, 0.48; 95% CI, 0.26-0.86; P=0.014) (73). In addition, the CNS ORRs were 66 and 43% in patients with measurable and/or non-measurable CNS lesions [odds ratio (OR) 2.5; 95% CI, 1.2-5.2; P=0.011] treated with osimertinib and standard EGFR-TKIs, respectively. CNS progression was lower in the osimertinib group (20%) than in the standard EGFR-TKI group (39%), whereas CNS progression from new CNS lesions was reported in 12% patients in the osimertinib group and 30% patients in the standard EGFR-TKI group. Thus, unlike other EGFR-TKIs, osimertinib not only decreases, but also prevents CNS progression. Having demonstrated a better efficacy and comparable tolerability in patients with CNS metastases, osimertinib can defer the need for whole-brain radiotherapy, which is associated with AEs and may not improve survival or quality of life (74,75). Empirical evidence from a real-world study revealed clinically meaningful CNS efficacy of osimertinib, with more than half of patients with EGFR T790M NSCLC and CNS metastases responding to treatment (response rate 59%; 95% CI, 55-62%) (76). Similarly, a recent meta-analysis demonstrated the effectiveness and safety of osimertinib for patients with intracranial metastatic disease with CNS ORR of 64%, CNS disease control rate of 90%, complete intracranial response rates of 7-23%, and a median best decrease in intracranial lesion size of -40 to -64% (77). Leptomeningeal metastases (LM), occurring in approximately 9% of EGFRm cases, (double of that among NSCLC population), further intensify the burden of CNS metastasis. The phase I, open-label BLOOM study demonstrated that osimertinib exhibited clinically meaningful efficacy and manageable safety in patients with EGFRm NSCLC and cytologically confirmed LM who had progressed on EGFR-TKIs. The study reported an ORR of 41% with a median duration of response of 15.2 months. The median PFS and OS were 8.6 months (95% CI, 5.4-13.7 months) and 11.0 months (95% CI, 8.0-18.0 months), respectively. Osimertinib also led to an improvement of neurological symptoms and CSF clearance in 57 and 28% of the patients, respectively (78). Similar results were elucidated by the AURA LM analysis, which exhibited a median LM PFS and OS of 11.1 months (95% CI 4.6-Not calculable) and 18.8 months (95% CI, 6.3-NC), respectively (79). Recent evidence from phase II and real-world studies also suggest that osimertinib may be a promising treatment option for EGFRm NSCLC with brain metastases and LM, regardless of the T790M mutation status (80,81).

Table IV. Summary of results for time to first and second subsequent therapy from the FLAURA study.

Time to therapy and patients in the study	Osimertinib	Standard EGFR-TKI	Hazard ratio (95% CI)
Time to first subsequent therapy or mortality (median time in months, 95% CI)	25.5 (22.0-29.1)	13.7 (12.3-15.7)	0.48 (0.39-0.58); P<0.0001
Time to second subsequent therapy or mortality (median time in months, 95% CI)	31.1 (28.8-35.9)	23.4 (20.0-25.6)	0.69 (0.56-0.84); P=0.0003
Patients remaining on initial study treatment			
12 months	69.5%	47.3%	
24 months	42.3%	16.2%	
36 months	28.0%	9.4%	

CI, confidence interval, EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor.

6. Safety profile of osimertinib

Alongside better clinical efficacy, osimertinib has demonstrated a favorable and consistent toxicity profile in the FALURA study. Despite almost twice the length of therapy (median exposure: Osimertinib, 20.7 months; EGFR-TKI, 11.5 months), fewer patients in the osimertinib group experienced grade ≥3 AEs compared with the comparator EGFR-TKI (42 vs. 47%) or discontinued treatment due to AEs (15 vs. 18%) (71). The most common AEs in patients treated with osimertinib were diarrhea (60%), rash (59%), nail toxicity (39%), dry skin (38%) and stomatitis (29%). Interstitial lung disease (ILD) was reported in 11 patients (4%) in the osimertinib group and 6 (2%) in the standard EGFR-TKI group; however, no fatal events of ILD were reported in either group. Severe AEs of ILD occurred in 6 patients (2%) in the osimertinib arm and in 4 (1%) in the comparator arm. Few patients had a fatal AE; 9 (3%) in the osimertinib group and 10 (4%) in the comparator arm. However, none of the deaths in the osimertinib arm and 2 in the comparator arm were related to the treatment.

7. Subsequent therapies

The proportion of patients remaining on first-line study treatment after 3 years was higher for osimertinib (28%) than for standard EGFR-TKIs (9%) (Table IV) (71). The median time (months) to first subsequent treatment was longer for osimertinib (25.5 months; 95% CI 22.0-29.1) than for standard EGFR-TKIs (13.7 months; 95% CI 12.3-15.7) (HR 0.48; 95% CI 0.393-0.581; P<0.0001) (Table IV) (71). This is a crucial indirect measure highlighting how long patients can potentially benefit from first-line osimertinib, and can remain on a well-tolerated treatment. Moreover, 31% patients in the osimertinib group did not receive any subsequent cancer treatment, while 48% received first subsequent anticancer treatment, primarily chemotherapy (Table IV) (71). A higher proportion (65%) in the standard EGFR-TKI group received first subsequent anticancer treatment, of which 47% received osimertinib. Additionally, 72 patients (26%) in the osimertinib group and 92 patients (33%) in the comparator group received a second subsequent therapy.

8. Clinical decision making

To maximize the clinical benefit of the different EGFR-TKIs, it is imperative to strategize their optimal sequencing (82,83). There is currently no evidence to ascertain at diagnosis the patients who are likely to develop T790M following treatment with first- or second-generation EGFR-TKIs. In many developing countries, T790M testing is not routinely conducted. Moreover, not all patients who progress on first-line EGFR-TKIs will receive a subsequent second-line treatment because of declining functional status. The results from previous EGFR-TKI trials have revealed that only few patients received post-progression treatment; the FLAURA study demonstrated that 30% patients in both groups received no subsequent therapy. Additionally, tissue or liquid biopsies are not always feasible or successful owning to challenges of tissue accessibility and patient performance status (84). In this regard, the dual-pronged approach of osimertinib, including a beneficial first-line therapeutic strategy for TKI-naive patients with NSCLC and as second-line standard therapy in patients with EGFR T790M mutations, irrespective of CNS metastasis, can be favorable (85). A network meta-analysis of 25 studies revealed that osimertinib seemed to be the most preferable first-line treatment in advanced EGFR-mutated NSCLC (86). Compelling evidence from the FLAURA study has demonstrated that the clinically and statistically significant PFS and intracranial efficacy benefit of osimertinib is compounded by an extended median OS, with a 20% reduction in risk of death and 52% reduction in risk of CNS progression (71). Longer duration to first subsequent treatment, along with acceptable toxicity and better quality of life outcomes, has placed osimertinib as a favorable option in the first-line setting for patients with EGFRm NSCLC. The recently released guidelines by both ESMO and NCCN have also recommended first-line osimertinib as a preferred option for patients with EGFRm, regardless of T790M mutation (Fig. 1) (13,14). A cost-effectiveness analysis of osimertinib in the first-line treatment of advanced EGFRm NSCLC using a Markov cohort model estimated that osimertinib was more effective in terms of quality-adjusted life-year gained than comparators (erlotinib-gefitinib) (87). A real-world study among EGFRm patients has demonstrated comparable health utility scores and toxicity profiles between osimertinib and gefitinib. This

Table V. Combination trials with EGFR-TKIs.

Name of study or Author	Trial arms	Efficacy results	Safety outcomes	(Refs.)
NEJ009	Gefitinib monotherapy (G) to combination therapy with gefitinib, carboplatin, and pemetrexed (GCP)	• GCP demonstrated significantly better PFS compared with G, no difference in PFS2 between the arms • Median OS GCP. 52.2 months; G, 38.8 months; HR, 0.695; P=0.013	Not available	(91)
RELAY	Erlotinib (ERL) in combination with ramucirumab (RAM) or placebo (PL)	• PFS: HR, 0.591 (95% CI, 0.461-0.760); P<0.0001 • PFS 2: HR, 0.690; 95% CI, 0.490-0.972; P=0.0325	Grade ≥3 AEs RAM, 72% PL, 54%	(92)
Noronha *et al*, 2019	Gefitinib (gef) or gefitinib with pemetrexed and carboplatin	• Estimated median PFS gef + C: 16 months; 95% CI, 13.7-18.3; gef: 8 months; 95% CI, 7.1-8.9 • HR for disease progression or mortality, 0.5; 95% CI, 0.39-0.65; P<0.001 • Estimated median OS gef + C: not reached gef: 18 months; 95% CI, 14.28-21.72 HR, 0.45; 95% CI, 0.31-0.66; P<0.001	AEs grade ≥3: gef + C, 51%; gef, 25%; P<0.001	(93)
NEJ026	Erlotinib plus bevacizumab 15 or erlotinib monotherapy.	Median PFS erlotinib plus bevacizumab group, 16.9 months (95% CI, 14.2-21.0) vs. erlotinib group, 13.3 months (11.1-15.3l) (HR, 0.605; 95% CI, 0.417-0.877; P=0·016)	• Grade ≥3 AEs erlotinib plus bevacizumab, 88%; erlotinib alone, 46% • Severe AEs (grade 4 neutropenia and grade 4 hepatic dysfunction) erlotinib plus bevacizumab, 8%; erlotinib alone, 4%	(94)

AE, adverse event; CI, confidence interval; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

supports the more favorable safety profile of osimertinib for guiding economic analyses going forward (88).

9. Future perspectives

In this era of precision medicine, optimized treatment sequencing and enhanced patient selection accounting for clinical and molecular characterization form the cornerstone for improved patient outcomes. The development of patient-centric strategies comprising of potent therapies, such as osimertinib, alone or together with other combination drugs, is crucial for attaining the ultimate goal of clinical outcomes. Furthermore, monitoring disease evolution using liquid biopsy is important to evaluate changes in circulating tumor DNA, mutation burden, the detection of cancer progression, and the development of drug resistance (89). Met amplification is the most common resistance mechanism to osimertinib therapy (first-line, 7-15%; second-line, 5-50%) alongside other mechanisms, such as C797S (first-line, 7%; second-line, 10-26%) and PIK3CA mutations (first-line, 7%; second-line, 5%) (90). The identification of targeted treatment options following the failure of osimertinib and T790M-independent acquired resistance to first- and second-generation EGFR-TKIs is an unmet medical need. The current NCCN guidelines recommended continuing osimertinib or switching to first-line systemic therapy for patients progressing on first-line osimertinib (Fig. 1) (14). An enhanced understanding on the resistance mechanisms with first-line osimertinib and potential combination strategies may help delay the resistance and provide therapeutic benefits after resistance is acquired. Apart from *EGFR*, the upregulation of other oncogenic pathways acts as a common resistance mechanism to tyrosine-kinase inhibition. Multiple clinical studies are evaluating EGFR-TKIs (including osimertinib) in combination with agents targeting pathways, such as MET, MAPK, BCL-2, and JAK activation. The NEJ009 trial, a single country study from Japan, demonstrated a significantly better PFS, with a longer median survival time (52.2 months) for the combination therapy of gefitinib with carboplatin and pemetrexed, compared with gefitinib monotherapy (38.8 months; HR, 0.695; P=0.013) (Table V) (91). Similarly, the RELAY study reported a significantly prolonged PFS with the combination therapy of ramucirumab plus erlotinib (Table V) (92). However, few studies of combination therapies with first-generation TKIs have reported PFS benefit at the cost of increased toxicity (Table V) (93,94). In this regard, the combination with osimertinib may be deemed favorable. Osimertinib has been combined with JAK 1 inhibitors, interrupting signaling of the JAK/STAT pathway, in a second-line study in T790M-mutant patients (95). Several other phase 1 and 2 clinical trials are currently evaluating the efficacy of osimertinib with combination drugs such as dasatinib, sapanisertib, glutaminase inhibitor CB-839 hydrochloride, necitumumab, navitoclax, and anlotinib (96-101). ORCHARD, a phase 2 platform study in patients with advanced NSCLC and disease progression on first-line osimertinib therapy, is evaluating the efficacy and safety of osimertinib with savolitinib, gefitinib, and necitumumab (102). An early phase study to assess combination therapy of osimertinib with brigatinib that prolong the C797S/T790M/activating-mutation-mediated resistance to osimertinib is underway (103). Furthermore, studies to assess combination therapies with osimertinib with chemotherapy (FLAURA 2) in patients with metastases, and savolitinib (SAVANNAH) to address MET resistance (after prior osimertinib therapy) are ongoing (104,105).

10. Conclusion

A better understanding of the involved genomic mechanisms in NSCLC has paved the way for target pathways and multiple treatment approaches. Patient characterization, precision therapy tailored according to the patient risk, regular monitoring for disease progression, and overcoming resistance are imperative to improve survival in patients with advanced NSCLC. While a number of the recent clinical trials for NSCLC have PFS as the designated surrogate endpoint for OS, its validity has been questioned, particularly when the magnitude of PFS benefit is limited. OS is an unambiguous and reliable endpoint providing confirmatory evidence of drug efficacy for improving patient survival. The FLAURA study with osimertinib is the first trial that has demonstrated clinically and statistically significant PFS, intracranial efficacy, and a statistically significant OS benefit compared with standard EGFR-TKIs. The median OS benefit of greater than 3 years sets a new benchmark for osimertinib and provides a window of opportunity for the management of patients with stage IV NSCLC with sensitizing mutation. This reaffirms the importance of osimertinib as the first-line therapy. In addition, osimertinib may be a promising treatment option for EGFR-mutated NSCLC with brain metastases and LM, regardless of T790M mutation status. Combination approaches with first-line osimertinib along with anticancer drugs may help address the issue of resistance to EGFR-TKIs.

Acknowledgments

The authors would like to thank AstraZeneca Pharma India Ltd. and Dr Piyalee Pal and Mrs. Neelam Joglekar from Covance Scientific Services & Solutions Pvt. Ltd., Pune for providing medical writing support that was funded by AstraZeneca in accordance with GPP3 guidelines.

Funding

The present manuscript was funded by AstraZeneca Pharma India Ltd.

Availability of data and materials

Not applicable.

Authors' contributions

AKV and AG conceptualized synthesized and interpreted the literature evidences for the manuscript. GM interpreted the literature evidences, reviewed, revised, and edited the manuscript for scientific content. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

GM is an employee of AstraZeneca Pharma India Ltd.

References

1. Zhang YL, Yuan JQ, Wang KF, Fu XH, Han XR, Threapleton D, Yang ZY, Mao C and Tang JL: The prevalence of EGFR mutation in patients with non-small cell lung cancer: A systematic review and meta-analysis. Oncotarget 7: 78985-78993, 2016.
2. Midha A, Dearden S and McCormack R: EGFR mutation incidence in non-small-cell lung cancer of adenocarcinoma histology: A systematic review and global map by ethnicity (mutMapII). Am J Cancer Res 5: 2892-2911, 2015.
3. Chantharasamee J, Poungvarin N, Danchaivijitr P and Techawatanawanna S: Clinical outcome of treatment of metastatic non-small cell lung cancer in patients harboring uncommon EGFR mutation. BMC Cancer 19: 701, 2019.
4. Seshacharyulu P, Ponnusamy MP, Haridas D, Jain M, Ganti AK and Batra SK: Targeting the EGFR signaling pathway in cancer therapy. Expert Opin Ther Targets 16: 15-31, 2012.
5. Morgillo F, Della Corte CM, Fasano M and Ciardiello F: Mechanisms of resistance to EGFR-targeted drugs: Lung cancer. ESMO Open 1: e000060, 2016.
6. Barnes TA, O'Kane GM, Vincent MD and Leighl NB: Third-generation tyrosine kinase inhibitors targeting epidermal growth factor receptor mutations in non-small cell lung cancer. Front Oncol 7: 113, 2017.
7. Nosaki K, Satouchi M, Kurata T, Yoshida T, Okamoto I, Katakami N, Imamura F, Tanaka K, Yamane Y, Yamamoto N, *et al*: Re-biopsy status among non-small cell lung cancer patients in Japan: A retrospective study. Lung Cancer 101: 1-8, 2016.
8. Arcila ME, Oxnard GR, Nafa K, Riely GJ, Solomon SB, Zakowski MF, Kris MG, Pao W, Miller VA and Ladanyi M: Rebiopsy of lung cancer patients with acquired resistance to EGFR inhibitors and enhanced detection of the T790M mutation using a locked nucleic acid-based assay. Clin Cancer Res 17: 1169-1180, 2011.
9. Takezawa K, Pirazzoli V, Arcila ME, Nebhan CA, Song X, de Stanchina E, Ohashi K, Janjigian YY, Spitzler PJ, Melnick MA, *et al*: HER2 amplification: A potential mechanism of acquired resistance to EGFR inhibition in EGFR-mutant lung cancers that lack the second-site EGFRT790M mutation. Cancer Discov 2: 922-933, 2012.
10. Scott LJ: Osimertinib as first-line therapy in advanced NSCLC: A profile of its use. Drugs Ther Perspect 34: 351-357, 2018.
11. Kujtan L and Subramanian J: Epidermal growth factor receptor tyrosine kinase inhibitors for the treatment of non-small cell lung cancer. Expert Rev Anticancer Ther 19: 547-559, 2019.
12. Imai H, Kaira K and Minato K: Clinical significance of post-progression survival in lung cancer. Thorac Cancer 8: 379-386, 2017.
13. Planchard D, Popat S, Kerr K, Novello S, Smit EF, Faivre-Finn C, Mok TS, Reck M, Van Schil PE, Hellmann MD, *et al*: Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 29 (Suppl 4): iv192-iv237, 2018.
14. Ettinger DS, Wood DE, Aggarwal C, Aisner DL, Akerley W, Bauman JR, Bharat A, Bruno DS, Chang JY, Chirieac LR, *et al*: NCCN Guidelines Insights: Non-small cell lung cancer, version 1.2020. J Natl Compr Canc Netw 17: 1464-1472, 2019.
15. Rajappa S, Krishna MV and Narayanan P: Integrating osimertinib in clinical practice for non-small cell lung cancer treatment. Adv Ther 36: 1279-1290, 2019.
16. Hsu WH, Yang JC, Mok TS and Loong HH: Overview of current systemic management of EGFR-mutant NSCLC. Ann Oncol 29 (Suppl 1): i3-i9, 2018.
17. U.S. Food and drug administration: Center for Drug Evaluation and Research: Approval letter IRESSA, NDA21-399, 2003. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/21-399_IRESSA_Approv.pdf.
18. 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.
19. Fukuoka M, Wu YL, Thongprasert S, Sunpaweravong P, Leong SS, Sriuranpong V, Chao TY, Nakagawa K, Chu DT, Saijo N, *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.
20. Mitsudomi T, Morita S, Yatabe Y, Negoro S, Okamoto I, Tsurutani J, Seto T, Satouchi M, Tada H and Hirashima T: 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.
21. Yoshioka H, Mitsudomi T, Morita S, Yatabe Y, Negoro S, Okamoto I, Seto T, Satouchi M, Tada H, Hirashima T, *et al*: Final overall survival results of WJTOG 3405, a randomized phase 3 trial comparing gefitinib (G) with cisplatin plus docetaxel (CD) as the first-line treatment for patients with non-small cell lung cancer (NSCLC) harboring mutations of the epidermal growth factor receptor (EGFR). J Clin Oncol 32 (Suppl 15): S8117, 2014.
22. Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, Gemma A, Harada M, Yoshizawa H, Kinoshita I, *et al*: Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med 362: 2380-2388, 2010.
23. Inoue A, Kobayashi K, Maemondo M, Sugawara S, Oizumi S, Isobe H, Gemma A, Harada M, Yoshizawa H, Kinoshita I, *et al*: Updated overall survival results from a randomized phase III trial comparing gefitinib with carboplatin-paclitaxel for chemo-naïve non-small cell lung cancer with sensitive EGFR gene mutations (NEJ002). Ann Oncol 24: 54-59, 2013.
24. 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 forpatients 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.
25. Zhou C, Wu YL, Chen G, Feng J, Liu XQ, Wang C, Zhang S, Wang J, Zhou S, Ren S, *et al*: Final overall survival results from a randomised, phase III study of erlotinib versus chemotherapy as first-line treatment of EGFR mutation-positive advanced non-small-cell lung cancer (OPTIMAL, CTONG-0802). Ann Oncol 26: 1877-1883, 2015.
26. 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.
27. Leon LF, Golsorkhi A, Liu S, Drozdowskyj A and Rosell R: Overall survival analyses of first-line erlotinib versus chemotherapy in the EURTAC study population controlling for the use of post-study therapy. Ann Oncol 25 (Suppl 4): iv426-iv470, 2014.
28. Wu YL, Zhou C, Liam CK, Wu G, Liu X, Zhong Z, Lu S, Cheng Y, Han B, Chen L, *et al*: First-line erlotinib versus gemcitabine/cisplatin in patients with advanced EGFR mutation-positive non-small-cell lung cancer: Analyses from the phase III, randomized, open-label, ENSURE study. Ann Oncol 26: 1883-1889, 2015.
29. 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.
30. 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.

31. 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, randomised phase 3 trial. Lancet Oncol 15: 213-222, 2014.
32. Mok TS, Wu YL, Ahn MJ, Garassino MC, Kim HR, Ramalingam SS, Shepherd FA, He Y, Akamatsu H, Theelen WS, *et al*: Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. N Engl J Med 376: 629-640, 2017.
33. Papadimitrakopoulou VA, Mok TS, Han JY, Ahn MJ, Delmonte A, Ramalingam SS, Kim SW, Shepherd FA, Laskin J, He 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 S0923-7534: 42155-42156, 2020.
34. 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.
35. Paz-Ares L, Tan EH, O'byrne K, Zhang L, Hirsh V, Boyer M, Yang JH, 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.
36. Wu YL, Cheng Y, Zhou X, Lee KH, Nakagawa K, Niho S, Tsuji F, Linke R, Rosell R, Corral J, *et al*: Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): A randomised, open-label, phase 3 trial. Lancet Oncol 18: 1454-1466, 2017.
37. 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 gefitinib in patients with advanced non-small-cell lung cancer and EGFR-activating mutations. J Clin Oncol 36: 2244-2250, 2018.
38. U.S. Food and Drug Administration, Center for Drug Evaluation and Research: NDA multi-disciplinary review and evaluation, 211288Orig1s000, VIZIMPRO/dacomitinib, 2018. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/211288Orig1s000MultidisciplineR.pdf.
39. Sequist LV, Waltman BA, Dias-Santagata D, Digumarthy S, Turke AB, Fidias P, Bergethon K, Shaw AT, Gettinger S, Cosper AK, *et al*: Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. Sci Transl Med 3: 75ra26, 2011.
40. Yu HA, Arcila ME, Rekhtman N, Sima CS, Zakowski MF, Pao W, Kris MG, Miller VA, Ladanyi M and Riely GJ: Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. Clin Cancer Res 19: 2240-2247, 2013.
41. Koyyala VP, Batra U, Jain P, Sharma M, Goyal P, Medisetty P, Jajodia A and Maheshwari UD: Frequency of T790M mutations after progression on epidermal growth factor receptor tyrosine kinase inhibitor in metastatic non-small cell lung cancer in Indian patients: Real-time data from tertiary cancer hospital. Lung India 35: 390-394, 2018.
42. Oxnard GR, Arcila ME, Sima CS, Riely GJ, Chmielecki J, Kris MG, Pao W, Ladanyi M and Miller VA: Acquired resistance to EGFR tyrosine kinase inhibitors in EGFR-mutant lung cancer: Distinct natural history of patients with tumors harboring the T790M mutation. Clin Cancer Res 17: 1616-1622, 2011.
43. Jaiswal R, Pinninti R, Krishna Mohan MV, Santa A, Boyella PK, Nambaru L, Murthy SS, Chowdary KV and Rajappa S: T790M mutation and clinical outcomes with osimertinib in patients with epidermal growth factor receptor-mutant non-small cell lung cancer. Indian J Med Paediatr Oncol 40: 73-78, 2019.
44. Westover D, Zugazagoitia J, Cho BC, Lovly 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.
45. Rangachari D, Yamaguchi N, VanderLaan PA, Folch E, Mahadevan A, Floyd SR, Uhlmann EJ, Wong ET, Dahlberg SE, Huberman MS and Costa DB: Brain metastases in patients with EGFR-mutated or ALK-rearranged non-small-cell lung cancers. Lung Cancer 88: 108-111, 2015.
46. Ali A, Goffin JR, Arnold A and Ellis PM: Survival of patients with non-small-cell lung cancer after a diagnosis of brain metastases. Curr Oncol 20: e300-e306, 2013.
47. Peters S, Bexelius C, Munk V and Leighl N: The impact of brain metastasis on quality of life, resource utilization and survival in patients with non-small-cell lung cancer. Cancer Treat Rev 45: 139-162, 2016.
48. Heon S, Yeap BY, Lindeman NI, Joshi VA, Butaney M, Britt GJ, Costa DB, Rabin MS, Jackman DM and Johnson BE: The impact of initial gefitinib or erlotinib versus chemotherapy on central nervous system progression in advanced non-small cell lung cancer with EGFR mutations. Clin Cancer Res 18: 4406-4414, 2012.
49. Omuro AM, Kris MG, Miller VA, Franceschi E, Shah N, Milton DT and Abrey LE: High incidence of disease recurrence in the brain and leptomeninges in patients with nonsmall cell lung carcinoma after response to gefitinib. Cancer 103: 2344-2348, 2005.
50. Chen YH, Chen YF, Chen CY, Shih JY and Yu CJ: Clinical factors associated with treatment outcomes in EGFR mutant non-small cell lung cancer patients with brain metastases: A case-control observational study. BMC Cancer 19: 1006, 2019.
51. Hoffknecht P, Tufman A, Wehler T, Pelzer T, Wiewrodt R, Schütz M, Serke M, Stöhlmacher-Williams J, Märten A, Maria Huber R, *et al*: Efficacy of the irreversible ErbB family blocker afatinib in epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI)-pretreated non-small-cell lung cancer patients with brain metastases or leptomeningeal disease. J Thorac Oncol 10: 156-163, 2015.
52. Doval DC, Desai CJ and Sahoo TP: Molecularly targeted therapies in non-small cell lung cancer: The evolving role of tyrosine kinase inhibitors. Indian J Cancer 56 (Suppl): S23-S30, 2019.
53. Shah RR and Shah DR: Safety and tolerability of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors in oncology. Drug Saf 42: 181-198, 2019.
54. Tan CS, Kumarakulasinghe NB, Huang YQ, Ang YLE, Choo JR, Goh BC and Soo RA: Third generation EGFR TKIs: Current data and future directions. Mol Cancer 17: 29, 2018.
55. Finlay MR, Anderton M, Ashton S, Ballard P, Bethel PA, Box MR, Bradbury RH, Brown SJ, Butterworth S, Campbell A, *et al*: Discovery of a potent and selective EGFR inhibitor (AZD9291) of both sensitizing and T790M resistance mutations that spares the wild type form of the receptor. J Med Chem 57: 8249-8267, 2014.
56. Murtuza A, Bulbul A, Shen JP, Keshavarzian P, Woodward BD, Lopez-Diaz FJ, Lippman SM and Husain H: Novel third-generation EGFR tyrosine kinase inhibitors and strategies to overcome therapeutic resistance in lung cancer. Cancer Res 79: 689-698, 2019.
57. Liu S, Li S, Hai J, Wang X, Chen T, Quinn MM, Gao P, Zhang Y, Ji H, Cross DAE and Wong KK: Targeting HER2 aberrations in non-small cell lung cancer with osimertinib. Clin Cancer Res 24: 2594-2604, 2018.
58. U.S. Food and Drug Administration, Center for Drug Evaluation and Research: Application number: 208065Orig1s000, Tagrisso/osimertinib. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/208065Orig1s000SumR.pdf. Accessed September 4, 2019.
59. Jänne PA, Yang JC, Kim DW, Planchard D, Ohe Y, Ramalingam SS, Ahn MJ, Kim SW, Su WC, Horn L, *et al*: AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. N Engl J Med 372: 1689-1699, 2015.
60. Goss G, Tsai CM, Shepherd FA, Bazhenova L, Lee JS, Chang GC, Crino L, Satouchi M, Chu Q, Hida T, *et al*: Osimertinib for pretreated EGFR Thr790Met-positive advanced non-small-cell lung cancer (AURA2): A multicentre, open-label, single-arm, phase 2 study. Lancet Oncol 17: 1643-1652, 2016.
61. Yang JC, Ahn MJ, Kim DW, Ramalingam SS, Sequist LV, Su WC, Kim SW, Kim JH, Planchard D, Felip E, *et al*: Osimertinib in pretreated T790M-positive advanced non-small-cell lung cancer: AURA study phase II extension component. J Clin Oncol 35: 1288-1296, 2017.
62. U.S. Food and Drug Administration: Osimertinib (TAGRISSO). https://www.fda.gov/drugs/resources-information-approved-drugs/osimertinib-tagrisso.
63. Lee CK, Novello S, Rydén A, Mann H and Mok T: Patient-reported symptoms and impact of treatment with osimertinib versus chemotherapy in advanced non-small-cell lung cancer: The AURA3 trial. J Clin Oncol 36: 1853-1860, 2018.

64. 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.
65. U.S. Food and Drug Administration: FDA approves osimertinib for first-line treatment of metastatic NSCLC with most common EGFR mutations. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-osimertinib-first-line-treatment-metastatic-nsclc-most-common-egfr-mutations. Accessed September 5, 2019.
66. Cho BC, Chewaskulyong B, Lee KH, Dechaphunkul A, Sriuranpong V, Imamura F, Nogami N, Kurata T, Okamoto I, Zhou C, *et al*: Osimertinib versus standard of care EGFR TKI as first-line treatment in patients with EGFRm advanced NSCLC: FLAURA Asian subset. J Thorac Oncol 14: 99-106, 2019.
67. Soria JC, Massard C and Le Chevalier T: Should progression-free survival be the primary measure of efficacy for advanced NSCLC therapy? Ann Oncol 21: 2324-2332, 2010.
68. Pasalic D, McGinnis GJ, Fuller CD, Grossberg AJ, Verma V, Mainwaring W, Miller AB, Lin TA, Jethanandani A, Espinoza AF, *et al*: Progression-free survival is a suboptimal predictor for overall survival among metastatic solid tumour clinical trials. Eur J Cancer 136: 176-185, 2020.
69. U.S. Food and Drug Administration: Clinical trial endpoints for the approval of cancer drugs and biologics. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-trial-endpoints-approval-cancer-drugs-and-biologics. Accessed September 5, 2019.
70. Ellis LM, Bernstein DS, Voest EE, Berlin JD, Sargent D, Cortazar P, Garrett-Mayer E, Herbst RS, Lilenbaum RC, Sima C, *et al*: American society of clinical oncology perspective: Raising the bar for clinical trials by defining clinically meaningful outcomes. J Clin Oncol 32: 1277-1280, 2014.
71. 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.
72. Mok T, Ahn MJ, Han JY, Kang JH, Katakami N, Kim H, Hodge R, Ghiorghiu DC, Cantarini M, Wu YL, *et al*: CNS response to osimertinib in patients (pts) with T790M-positive advanced NSCLC: Data from a randomized phase III trial (AURA3). J Clin Oncol 35 (15_Suppl): S9005, 2017.
73. Reungwetwattana T, Nakagawa K, Cho BC, Cobo M, Cho EK, Bertolini A, Bohnet S, Zhou C, Lee KH, Nogami N, *et al*: CNS response to osimertinib versus standard epidermal growth factor receptor tyrosine kinase inhibitors in patients with untreated EGFR-mutated advanced non-small-cell lung cancer. J Clin Oncol: JCO2018783118, 2018 doi: 10.1200/JCO.2018.78.3118 (Epub ahead of print).
74. Monaco EA III, Faraji AH, Berkowitz O, Parry PV, Hadelsberg U, Kano H, Niranjan A, Kondziolka D and Lunsford LD: Leukoencephalopathy after whole-brain radiation therapy plus radiosurgery versus radiosurgery alone for metastatic lung cancer. Cancer 119: 226-232, 2013.
75. Mulvenna P, Nankivell M, Barton R, Faivre-Finn C, Wilson P, McColl E, Moore B, Brisbane I, Ardron D, Holt T, *et al*: Dexamethasone and supportive care with or without whole brain radiotherapy in treating patients with non-small cell lung cancer with brain metastases unsuitable for resection or stereotactic radiotherapy (QUARTZ): Results from a phase 3, non-inferiority, randomised trial. Lancet 388: 2004-2014, 2016.
76. Metro G, Provencio M, Kim DW, Cho BC, Park K, Pan Y, Shi Y, Migliorino R, Tiseo M, Yu J, *et al*: Osimertinib in epidermal growth factor receptor (EGFR) T790M advanced non-small cell lung cancer (NSCLC): Analysis of patients with central nervous system (CNS) metastases in a real-world study (ASTRIS). Ann Oncol 30 (Suppl 5): v624, 2019.
77. Erickson AW, Brastianos PK and Das S: Assessment of effectiveness and safety of osimertinib for patients with intracranial metastatic disease: A systematic review and meta-analysis. JAMA Netw Open 3: e201617, 2020.
78. Yang JCH, Kim SW, Kim DW, Lee JS, Cho BC, Ahn JS, Lee DH, Kim TM, Goldman JW, Natale RB, *et al*: Osimertinib in patients with epidermal growth factor receptor mutation-positive non-small-cell lung cancer and leptomeningeal metastases: The BLOOM study. J Clin Oncol 38: 538-547, 2020.
79. Ahn MJ, Chiu CH, Cheng Y, Han JY, Goldberg SB, Greystoke A, Crawford J, Zhao Y, Huang X, Johnson M, *et al*: Osimertinib for patients with leptomeningeal metastases associated with EGFR T790M-positive advanced NSCLC: The AURA leptomeningeal metastases analysis. J Thorac Oncol 15: 637-648, 2020.
80. Park S, Lee MH, Seong M, Kim ST, Kang JH, Cho BC, Lee KH, Cho EK, Sun JM, Lee SH, *et al*: A Phase II, multicenter, two cohort study of 160 mg osimertinib in EGFR T790M-positive non-small cell lung cancer patients with brain metastases or leptomeningeal disease who progressed on prior EGFR TKI therapy. Ann Oncol 31: 1397-1404, 2020.
81. Lee J, Choi Y, Han J, Park S, Jung HA, Su JM, Lee SH, Ahn JS, Park K and Ahn MJ: Osimertinib improves overall survival in patients with EGFR-Mutated NSCLC with leptomeningeal metastases regardless of T790M mutational status. J Thorac Oncol 15: 1758-1766, 2020.
82. Girard N: Optimizing outcomes in EGFR mutation-positive NSCLC: Which tyrosine kinase inhibitor and when? Future Oncol 14: 1117-1132, 2018.
83. Gelatti ACZ, Drilon A and Santini FC: Optimizing the sequencing of tyrosine kinase inhibitors (TKIs) in epidermal growth factor receptor (EGFR) mutation-positive non-small cell lung cancer (NSCLC). Lung Cancer 137: 113-122, 2019.
84. Kawamura T, Kenmotsu H, Taira T, Omori S, Nakashima K, Wakuda K, Ono A, Naito T, Murakami H, Mori K, *et al*: Rebiopsy for patients with non-small-cell lung cancer after epidermal growth factor receptor-tyrosine kinase inhibitor failure. Cancer Sci 107: 1001-1005, 2016.
85. Shah R and Lester JF: Tyrosine kinase inhibitors for the treatment of EGFR mutation-positive non-small-cell lung cancer: A clash of the generations. Clin Lung Cancer 21: e216-e228, 2020.
86. Zhang H, Chen J, Liu T, Dang J and Li G: First-line treatments in EGFR-mutated advanced non-small cell lung cancer: A network meta-analysis. PLoS One 14: e0223530, 2019.
87. Aguilar-Serra J, Gimeno-Ballester V, Pastor-Clerigues A, Milara J, Marti-Bonmati E, Trigo-Vicente C, Alós-Almiñana M and Cortijo J: Osimertinib in first-line treatment of advanced EGFR-mutated non-small-cell lung cancer: A cost-effectiveness analysis. J Comp Eff Res 8: 853-863, 2019.
88. Jiang SX, Walton RN, Hueniken K, Baek J, McCartney A, Labbé C, Smith E, Chan SW, Chen R, Brown C, *et al*: Real-world health utility scores and toxicities to tyrosine kinase inhibitors in epidermal growth factor receptor mutated advanced non-small cell lung cancer. Cancer Med 8: 7542-7555, 2019.
89. Schuler M: Liquid biopsies for dynamic monitoring of EGFR mutations in lung cancer. J Thorac Oncol 12 (Suppl): S85, 2017.
90. Leonetti A, Sharma S, Minari R, Perego P, Giovannetti E and Tiseo M: Resistance mechanisms to osimertinib in EGFR-mutated non-small cell lung cancer. Br J Cancer 121: 725-737, 2019.
91. Nakamura A, Inoue A, Morita S, Hosomi Y, Kato T, Fukuhara T, Gemma A, Takahashi K, Fujita Y, Harada T, *et al*: Phase III study comparing gefitinib monotherapy (G) to combination therapy with gefitinib, carboplatin, and pemetrexed (GCP) for untreated patients (pts) with advanced non-small cell lung cancer (NSCLC) with EGFR mutations (NEJ009). J Clin Oncol 36 (15_suppl): S9005, 2018.
92. Nakagawa K, Garon EB, Seto T, Nishio M, Santiago PA, Chiu CH, Park K, Novello S, Nadal E, Imamura F, *et al*: RELAY: A multinational, double-blind, randomized Phase 3 study of erlotinib (ERL) in combination with ramucirumab (RAM) or placebo (PL) in previously untreated patients with epidermal growth factor receptor mutation-positive (EGFRm) metastatic non-small cell lung cancer (NSCLC). J Clin Oncol 37 (15_Suppl): 9000, 2019.
93. Noronha V, Joshi A, Patil VM, Chougule A, Mahajan A, Janu A, Purandare N, Kumar R, More S, Goud S, *et al*: Phase III randomized trial comparing gefitinib to gefitinib with pemetrexed-carboplatin chemotherapy in patients with advanced untreated EGFR mutant non-small cell lung cancer (gef vs gef+ C). J Clin Oncol 37 (15_Suppl): S9001, 2019.
94. Saito H, Fukuhara T, Furuya N, Watanabe K, Sugawara S, Iwasawa S, Tsunezuka Y, Yamaguchi O, Okada M, Yoshimori K, *et al*: Erlotinib plus bevacizumab versus erlotinib alone in patients with EGFR-positive advanced non-squamous non-small-cell lung cancer (NEJ026): Interim analysis of an open-label, randomised, multicentre, phase 3 trial. Lancet Oncol 20: 625-635, 2019.
95. ClinicalTrials.gov: Assessing an oral janus kinase inhibitor, AZD4205, in combination with osimertinib in patients who have advanced non-small cell lung cancer (JACKPOT1). ClinicalTrials.gov Identifier: NCT03450330. https://clinicaltrials.gov/ct2/show/NCT03450330. Accessed March 1, 2018.

96. ClinicalTrials.gov: Dasatinib and osimertinib (AZD9291) in advanced non-small cell lung cancer with EGFR mutations. ClinicalTrials.gov Identifier: NCT02954523. https://clinicaltrials.gov/ct2/show/NCT02954523. Accessed November 3, 2016.
97. ClinicalTrials.gov: Testing the Combination of MLN0128 (TAK-228) and AZD9291 in Advanced EGFR (Epidermal Growth Factor Receptor) Mutation Positive Non-small Cell Lung Cancer. ClinicalTrials.gov Identifier: NCT02503722. https://clinicaltrials.gov/ct2/show/NCT02503722?term=osimertinib&cond=NSCLC+Stage+IV&rank=3. Accessed July 21, 2015.
98. ClinicalTrials.gov: Telaglenastat Hydrochloride and Osimertinib in Treating Patients With EGFR-Mutated Stage IV Non-small Cell Lung Cancer. ClinicalTrials.gov Identifier: NCT03831932. https://clinicaltrials.gov/ct2/show/NCT03831932?term=osimertinib&cond=NSCLC+Stage+IV&rank=6. Accessed February 6, 2019.
99. ClinicalTrials.gov: Osimertinib and Necitumumab in Treating Patients With EGFR-Mutant Stage IV or Recurrent Non-small Cell Lung Cancer Who Have Progressed on a Previous EGFR Tyrosine Kinase Inhibitor. ClinicalTrials.gov Identifier: NCT02496663. https://clinicaltrials.gov/ct2/show/NCT02496663?term=osimertinib&cond=NSCLC+Stage+IV&rank=7. Accessed July 14, 2015.
100. ClinicalTrials.gov: Study of anlotinib combined with osimertinib as second-line treatment in stage IIIb-IV NSCLC with confirmed EGFRm and T790M (ALTN-03). ClinicalTrials.gov Identifier: NCT04029350. https://clinicaltrials.gov/ct2/show/NCT04029350?term=osimertinib&cond=NSCLC+Stage+IV&rank=12. Accessed July 23, 2019.
101. ClinicalTrials.gov: Osimertinib and Navitoclax in treating patients with EGFR-positive previously treated advanced or metastatic non-small cell lung cancer. ClinicalTrials.gov Identifier: NCT02520778. https://clinicaltrials.gov/ct2/show/NCT02520778. Accessed August 13, 2015.
102. ClinicalTrials.gov: Phase 2 Platform Study in patients with advanced non-small lung cancer who progressed on first-line osimertinib therapy (ORCHARD) (ORCHARD). ClinicalTrials.gov Identifier: NCT03944772. https://www.clinicaltrials.gov/ct2/show/NCT03944772. Accessed May 10, 2019.
103. Uchibori K, Inase N, Araki M, Kamada M, Sato S, Okuno Y, Fujita N and Katayama R: Brigatinib combined with anti-EGFR antibody overcomes osimertinib resistance in EGFR-mutated non-small-cell lung cancer. Nat Commun 8: 14768, 2017.
104. ClinicalTrials.gov: A Study of Osimertinib With or Without Chemotherapy as 1st Line Treatment in Patients With Mutated Epidermal Growth Factor Receptor Non-Small Cell Lung Cancer (FLAURA2) (FLAURA2). ClinicalTrials.gov Identifier: NCT04035486. https://clinicaltrials.gov/ct2/show/NCT04035486?term=flaura+2&draw=2&rank=1. Accessed July 29, 2019.
105. Clinical trial.gov: Osimertinib Plus Savolitinib in EGFRm+/MET+ NSCLC Following Prior Osimertinib (SAVANNAH). ClinicalTrials.gov Identifier: NCT03778229. https://clinicaltrials.gov/ct2/show/NCT03778229?term=SAVANNAH&draw=2&rank=1. Accessed December 19, 2018.